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Europäisches Patentamt  
European Patent Office  
Office européen des brevets

(11) Publication number:

**0 166 591**  
**A2**

(12)

EUROPEAN PATENT APPLICATION

(21) Application number: 85304468.3

(51) Int. Cl.: **C 07 D 209/22, A 61 K 31/40**

(22) Date of filing: 24.06.85

(30) Priority: 25.06.84 US 624173

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(43) Date of publication of application: 02.01.86  
Bulletin 86/1

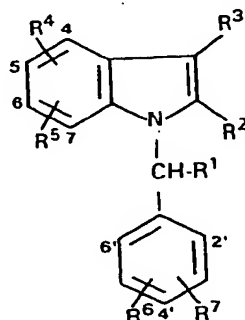
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(84) Designated Contracting States: **AT BE CH DE FR GB IT**  
**LI LU NL SE**

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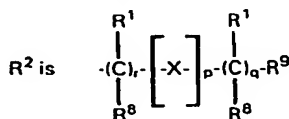
(54) **Indole-2-alkanolic acids and their use as prostaglandin antagonists.**

(57) Compounds of the formula I



where

R<sup>1</sup> is H or alkyl of 1 to 6 carbons or R<sup>1</sup> and R<sup>8</sup> taken together form a group (CH<sub>2</sub>)<sub>v</sub> wherein v is 1 to 7;



where

each R<sup>8</sup> is independently H, OH, C<sub>1</sub> to C<sub>4</sub>-O-alkyl or alkyl of 1 to 4 carbons; or an R<sup>1</sup> and an R<sup>8</sup> taken together form a group (CH<sub>2</sub>)<sub>v</sub> wherein v is 1 to 7,

R<sup>9</sup> is COOR<sup>1</sup>; CH<sub>2</sub>OH; CHO; tetrazole; NHSO<sub>2</sub>R<sup>10</sup> wherein R<sup>10</sup> is OH, alkyl or alkoxy of 1 to 6 carbons, perhaloalkyl of 1 to 6 carbons, phenyl or phenyl substituted by alkyl or alkoxy groups of 1 to 3 carbons, halogen, hydroxy, COOH, CN, formyl or acyl of 1 to 6 carbons; CONHSO<sub>2</sub>R<sup>10</sup>; hydroxymethylketone; CN; or CON(R<sup>8</sup>)<sub>2</sub>;

X is O; S; SO; SO<sub>2</sub>; NR<sup>11</sup> wherein R<sup>11</sup> is H, alkyl of 1 to 6 carbons, acyl of 1 to 6 carbons, CN; CR<sup>1</sup>R<sup>8</sup>;

or the unit  $\begin{array}{c} \text{R}^1 \\ | \\ \text{C} \\ | \\ \text{R}^8 \end{array}$  wherein the dotted line represents an optical triple bond and in which the R<sup>1</sup> and R<sup>8</sup> substituents are absent when a triple bond is present;

r and q are each independently 0 to 5 and p is 0 or 1 provided that the total of p, q and r is 2 to 6;

R<sup>3</sup> is H, alkyl of 1 to 6 carbons; phenyl or phenyl substituted by R<sup>4</sup>; or C<sub>1</sub> to C<sub>4</sub> alkylphenyl or C<sub>1</sub> to C<sub>4</sub> alkylphenyl in which the phenyl is substituted by R<sup>4</sup>;

R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup> and R<sup>7</sup> are each independently selected from:

(1) hydrogen;

(2) alkyl having 1 to 6 carbon atoms;

(3) alkenyl having 2 to 6 carbon atoms;

(4)  $-(CH_2)_nM$

wherein n is 0 to 3 and M is

a)  $OR^{12}$ ;

b) halogen;

c)  $CF_3$ ;

d)  $SR^{12}$ ;

e) phenyl or substituted phenyl wherein substituted phenyl is as defined below in the definition of  $R^{12}$ ;

f)  $COOR^{13}$ ;

$\begin{array}{c} O \\ || \end{array}$

g)  $C-R^{14}$ ;

h) tetrazole;

$\begin{array}{c} O \\ || \end{array}$

i)  $-NH-C-R^{15}$  wherein  $R^{15}$  is  $C_1$  to  $C_6$  alkyl, benzyl or phenyl;

j)  $-NR^{13}R^{13}$ ;

k)  $-NHSO_2R^{16}$  wherein  $R^{16}$  is  $C_1$  to  $C_6$  alkyl, phenyl, or  $CF_3$ ;

$\begin{array}{c} O \\ || \end{array}$

l)  $-C-CH_2OH$ ;

m)  $-SOR^{12}$ ;

n)  $-CON^{13}R^{13}$ ;

o)  $-SO_2NR^{13}R^{13}$ ;

p)  $-SO_2R^{12}$ ;

q)  $NO_2$ ;

$\begin{array}{c} O \\ || \end{array}$

r)  $O-C-R^{14}$ ;

$\begin{array}{c} O \\ || \end{array}$

s)  $O-C-NR^{13}R^{13}$ ;

$\begin{array}{c} O \\ || \end{array}$

t)  $O-C-OR^{15}$ ;

u) CN;

each  $R^{12}$  independently is H;  $C_1$  to  $C_6$  alkyl; benzyl; phenyl or substituted phenyl wherein the substituents are  $C_1$  to  $C_3$  alkyl, halogen, CN,  $CF_3$ ,  $COOR^{13}$ ,  $CH_2COOR^{13}$ ,  $C_1$  to  $C_3$  alkoxy, or  $C_1$  to  $C_4$  perfluoroalkyl;

each  $R^{13}$  is independently H, phenyl or  $C_1$  to  $C_6$  alkyl; and,

each  $R^{14}$  independently is H,  $(CH_2)_nCOOR^{13}$  wherein n is 0 to 4,  $C_1$  to  $C_6$  alkyl,  $CF_3$ , phenyl, or substituted phenyl wherein substituted phenyl is as defined above in the definition of  $R^{12}$ ;

and their pharmaceutically acceptable salts are useful as prostaglandin antagonists and are made into pharmaceutical compositions. Certain of the compounds are novel.

INDOLE-2-ALKANOIC ACIDS AND THEIR USE AS  
PROSTAGLANDIN ANTAGONISTS

5

This invention relates to prostaglandin antagonists useful in treating a variety of conditions, such as allergic asthma where excessive contractile activity of prostaglandins and prostaglandin biosynthetic intermediates occur.

10 These compounds antagonize the actions of contractile prostaglandins, such as  $\text{PGF}_{2\alpha}$ ,  $\text{PGG}_2$ ,  $\text{PGH}_2$ ,  $\text{PGD}_2$  and  $\text{TXA}_2$ . The use of agents which act as prostaglandin antagonists offers new approaches

15 to therapy in a number of disease states. For example, certain prostaglandins, such as  $\text{PGF}_{2\alpha}$ ,  $\text{PGD}_2$ ,  $\text{PGG}_2$ , and  $\text{PGH}_2$ , are potent contractants of bronchial muscle. Indeed human asthmatics have been shown to be especially sensitive to the

20 bronchial constricting action of  $\text{PGF}_{2\alpha}$ .

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The compounds of the present invention also produce antithrombotic effects. Thus, they are useful in the treatment and/or prevention of thromboembolic diseases such as arterial thrombosis.

5 In addition to the involvement of contractile prostaglandins in chronic obstructive lung disease (or asthma), prostaglandins are known to play a role in other allergic conditions, as well as inflammation, diarrhea, hypertension, angina,  
10 platelet aggregation, cerebral spasm, cerebral ischemia, myocardial ischemia, premature labor, spontaneous abortion, dysmenorrhea, glomerular nephritis, and systemic lupus erythematosus. Consequently, the compounds of this invention will  
15 alleviate the above mentioned diseases.

In addition to the prostaglandin antagonist actions, the compounds of this invention are inhibitors of the synthesis of leukotrienes. Leukotrienes B<sub>4</sub>, C<sub>4</sub>, D<sub>4</sub> and E<sub>4</sub> are known to  
20 contribute to various disease conditions such as asthma, psoriasis, inflammation, pain, ulcers and systemic anaphylaxis. Thus inhibition of the synthesis of such compounds will alleviate these disease states.

25 The compounds of the present invention may be used to treat or prevent mammalian (especially, human) disease states such as erosive gastritis; erosive esophagitis; inflammatory bowel disease; ethanol-induced hemorrhagic erosions; hepatic  
30 ischemia; noxious agent induced damage or necrosis of hepatic, pancreatic, renal, or myocardial tissue; liver parenchymal damage caused by hepatotoxic agents



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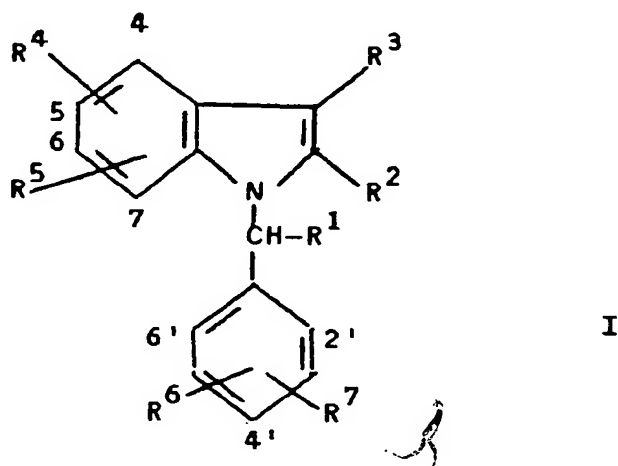
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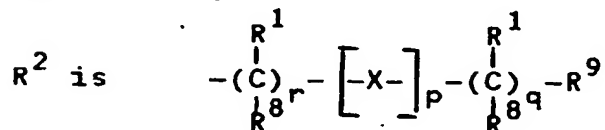
such as  $\text{CCl}_4$  and D-galactosamine; ischemic renal failure; disease-induced hepatic damage; bile salt induced pancreatic or gastric damage; trauma- or stress-induced cell damage; and glycerol-induced renal failure.

The present invention relates to a pharmaceutical composition comprising a compound of the Formula I:



wherein:

$R^1$  is H or alkyl of 1 to 6 carbons or  $R^1$  and  $R^8$  taken together form a group  $(\text{CH}_2)_v$  wherein  $v$  is 1 to 7;



wherein:

each  $R^8$  is independently H, OH,  $\text{C}_1$  to  $\text{C}_4$ -O-alkyl or alkyl of 1 to 4 carbons; or an  $R^1$  and an  $R^8$  taken together form a group  $(\text{CH}_2)_v$  wherein  $v$  is 1 to 7.

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$R^9$  is  $\text{COOR}^1$ ;  $\text{CH}_2\text{OH}$ ;  $\text{CHO}$ ; tetrazole;  
 $\text{NHSO}_2\text{R}^{10}$  wherein  $\text{R}^{10}$  is OH, alkyl or alkoxy of  
 1 to 6 carbons, perhaloalkyl of 1 to 6 carbons,  
 phenyl or phenyl substituted by alkyl or alkoxy  
 5 groups of 1 to 3 carbons, halogen, hydroxy,  $\text{COOH}$ ,  $\text{CN}$ ,  
 formyl or acyl to 1 to 6 carbons;  $\text{CONHSO}_2\text{R}^{10}$ ;  
 hydroxymethylketone;  $\text{CN}$ ; or  $\text{CON}(\text{R}^8)_2$ ;  
 $\text{X}$  is O; S; SO;  $\text{SO}_2$ ;  $\text{NR}^{11}$  wherein  $\text{R}^{11}$   
 is H, alkyl of 1 to 6 carbons, acyl of 1 to 6 carbons,  
 10  $\text{CN}$ ;  $\text{CR}^1\text{R}^8$ ;

or the unit  $\begin{array}{c} \text{R}^1 \quad \text{R}^8 \\ | \quad | \\ -\text{C}=\text{C}- \end{array}$  wherein the dotted line  
 represents an optional triple bond and in which the  
 $\text{R}^1$  and  $\text{R}^8$  substituents are absent when a triple  
 15 bond is present;

$r$  and  $q$  are each independently 0 to 5 and  $p$   
 is 0 or 1 provided that the total of  $p$ ,  $q$  and  $r$  is 2  
 to 6;

$\text{R}^3$  is H, alkyl of 1 to 6 carbons; phenyl  
 20 or phenyl substituted by  $\text{R}^4$ ; or  $\text{C}_1$  to  $\text{C}_4$  alkyl-  
 phenyl or  $\text{C}_1$  to  $\text{C}_4$  alkylphenyl in which the  
 phenyl is substituted by  $\text{R}^4$ ;

$\text{R}^4$ ,  $\text{R}^5$ ,  $\text{R}^6$  and  $\text{R}^7$  are each  
 independently selected from:

- 25 (1) hydrogen;  
 (2) alkyl having 1 to 6 carbon atoms;  
 (3) alkenyl having 2 to 6 carbon atoms;  
 (4)  $-(\text{CH}_2)_n\text{M}$   
 wherein  $n$  is 0 to 3 and  $\text{M}$  is  
 30 a)  $\text{OR}^{12}$ ;  
 b) halogen;  
 c)  $\text{CF}_3$ ;

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- d)  $\text{SR}^{12}$ ;  
 e) phenyl or substituted phenyl  
 wherein substituted phenyl is  
 as defined below in the  
 definition of  $\text{R}^{12}$ ;

10

- f)  $\text{COOR}^{13}$ ;  
 g)  $\begin{array}{c} \text{O} \\ | \\ \text{C}-\text{R}^{14} \end{array}$ ;  
 h) tetrazole;

15

- i)  $-\text{NH}-\begin{array}{c} \text{O} \\ || \\ \text{C} \end{array}-\text{R}^{15}$  wherein  $\text{R}^{15}$  is  
 $\text{C}_1$  to  $\text{C}_6$  alkyl, benzyl or  
 phenyl;  
 j)  $-\text{NR}^{13}\text{R}^{13}$ ;  
 k)  $-\text{NHSO}_2\text{R}^{16}$  wherein  $\text{R}^{16}$   
 is  $\text{C}_1$  to  $\text{C}_6$  alkyl,  
 phenyl, or  $\text{CF}_3$ ;

20

- l)  $-\begin{array}{c} \text{O} \\ || \\ \text{C} \end{array}-\text{CH}_2\text{OH}$ ;

25

- m)  $-\text{SOR}^{12}$ ;  
 n)  $-\text{CONR}^{13}\text{R}^{13}$ ;  
 o)  $-\text{SO}_2\text{NR}^{13}\text{R}^{13}$ ;  
 p)  $-\text{SO}_2\text{R}^{12}$ ;  
 q)  $\text{NO}_2$ ;

30

- r)  $\begin{array}{c} \text{O} \\ || \\ \text{O}-\text{C}-\text{R}^{14} \end{array}$ ;  
 s)  $\begin{array}{c} \text{O} \\ || \\ \text{O}-\text{C}-\text{NR}^{13}\text{R}^{13} \end{array}$ ;  
 t)  $\begin{array}{c} \text{O} \\ || \\ \text{O}-\text{C}-\text{OR}^{15} \end{array}$ ;  
 u)  $\text{CN}$ ;

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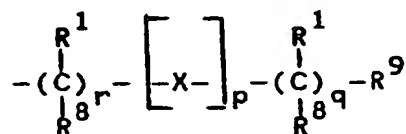
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- each  $R^{12}$  independently is H;  $C_1$  to  $C_6$  alkyl; benzyl; phenyl or substituted phenyl wherein the substituents are  $C_1$  to  $C_3$  alkyl, halogen, CN,  $CF_3$ ,  $COOR^{13}$ ,  $CH_2COOR^{13}$ ,  $C_1$  to  $C_3$  alkoxy, or  $C_1$  to  $C_4$  perfluoroalkyl;
- each  $R^{13}$  is independently H, phenyl or  $C_1$  to  $C_6$  alkyl; and,
- each  $R^{14}$  independently is H,  $(CH_2)_nCOOR^{13}$  wherein n is 0 to 4,  $C_1$  to  $C_6$  alkyl,  $CF_3$ , phenyl, or substituted phenyl wherein substituted phenyl is as defined above in the definition of  $R^{12}$ ; or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

- As used herein, the terms "each independently" or the equivalents thereof are employed to describe a number of possible position isomers and/or structural variations. For example, as described above,  $R^2$  is:

20



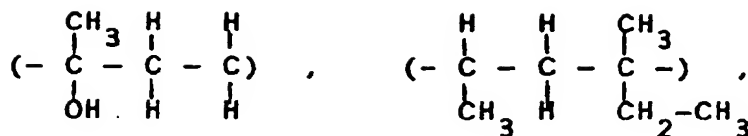
- The letters r and q, represent possible alkane chains of from 0 to 5 carbon atoms, each having the  $R^1$  and  $R^8$  substituent groups. On each carbon atom of the alkane chain, the  $R^1$  and/or  $R^8$  substituent may be different. The above description therefore contemplates structures such as the following for the segments  $-(CR^1R^8)_r-$  and  $-(CR^1R^8)_q-$ :

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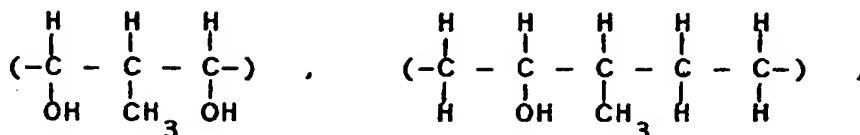
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The alkyl groups referred to above may be straight chain or branched or may include cycloalkyl groups. As used herein, the term "lower" as applied to alkyl, acyl, alkoxy and the like, unless stated otherwise refers to groups having 1 to 6 carbon atoms. Halogen or halo means fluoro, chloro, bromo and/or iodo.

Pharmaceutically acceptable salts of the compounds described herein are included within the scope of the present invention. Such salts may be prepared from pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from inorganic bases include sodium, potassium, lithium, ammonium, calcium, magnesium, ferrous, zinc, copper, manganous, aluminum, ferric, manganic salts and the like. Particularly preferred are the potassium, sodium calcium and magnesium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted

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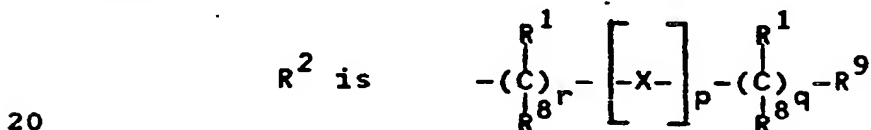
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amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, tri-methylamine, diethanolamine, diethylamine, triethylamine, tripropylamine, 5 ethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, tomethamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, imidazole, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines piperazine, 10 N,N-dibenzylethylenediamine, piperidine, N-ethylpiperidine, morpholine, N-ethylmorpholine, polyamine resins and the like.

Preferred compositions of the present invention comprise compounds of the Formula I wherein: 15 each  $R^1$  is H or alkyl of 1 to 6 carbons or  $R^1$  and  $R^8$  taken together form a group  $(CH_2)_v$  wherein v is 1 to 7;



wherein:

each  $R^8$  is independently H, OH,  $C_1$  to  $C_4$ -O-alkyl or alkyl of 1 to 4 carbons; or an  $R^1$  and an  $R^8$  taken together form a group  $(CH_2)_v$  25 wherein v is 1 to 7;  
 $R^9$  is  $COOR^1$ ;  $CH_2OH$ ; CHO; tetrazole;  $CONHSO_2R^{10}$  wherein  $R^{10}$  is OH, alkyl or alkoxy of 1 to 6 carbons, perhaloalkyl of 1 to 6 carbons, phenyl or phenyl substituted by alkyl or alkoxy 30 groups of 1 to 3 carbons, halogen, hydroxy, COOH, CN, formyl or acyl to 1 to 6 carbons; hydroxymethylketone; CN; or  $CON(R^8)_2$ ;

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X is O; S; SO; SO<sub>2</sub>; NR<sup>11</sup> wherein R<sup>11</sup> is H, alkyl of 1 to 6 carbons, acyl of 1 to 6 carbons, CN; CR<sup>1</sup>R<sup>8</sup>;

5. or the unit  $\begin{array}{c} \text{R}^1 \quad \text{R}^8 \\ | \quad | \\ -\text{C} \equiv \text{C}- \end{array}$  wherein the dotted line represents an optional triple bond and in which the R<sup>1</sup> and R<sup>8</sup> substituents are absent when a triple bond is present;

10. r and q are each independently 0 to 5 and p is 0 or 1 provided that the total of P, q and r is 2 to 4;

15. R<sup>3</sup> is H, alkyl of 1 to 6 carbons; phenyl or phenyl substituted by R<sup>4</sup>; or C<sub>1</sub> to C<sub>4</sub> alkyl-phenyl or C<sub>1</sub> to C<sub>4</sub> alkylphenyl in which the phenyl is substituted by R<sup>4</sup>;

R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup> and R<sup>7</sup> are each independently selected from:

- (1) hydrogen;
- (2) alkyl having 1 to 6 carbon atoms;
20. (3) alkenyl having 2 to 6 carbon atoms;
- (4)  $-(\text{CH}_2)_n^M$  wherein n is 0 or 1 and M is
  - a) OR<sup>12</sup>;
  - b) halogen;
  25. c) CF<sub>3</sub>;
  - d) SR<sup>12</sup>;
  - e) phenyl or substituted phenyl wherein substituted phenyl is as defined below in the definition of R<sup>12</sup>;
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f)  $\text{COOR}^{13}$ ;g)  $\text{C}(=\text{O})\text{-R}^{14}$ ;

h) tetrazole;

10

i)  $\text{-NH-C}(=\text{O})\text{-R}^{15}$  wherein  $\text{R}^{15}$  is  $\text{C}_1$  to  $\text{C}_6$  alkyl, benzyl or phenyl;j)  $\text{-NR}^{13}\text{R}^{13}$ ;k)  $\text{-NHSO}_2\text{R}^{16}$  wherein  $\text{R}^{16}$  is  $\text{C}_1$  to  $\text{C}_6$  alkyl, phenyl, or  $\text{CF}_3$ ;

15

l)  $\text{-C}(=\text{O})\text{-CH}_2\text{OH}$ ;m)  $\text{-SOR}^{12}$ ;n)  $\text{-CONR}^{13}\text{R}^{13}$ ;o)  $\text{-SO}_2\text{NR}^{13}\text{R}^{13}$ ;p)  $\text{-SO}_2\text{R}^{12}$ ;

20

q)  $\text{NO}_2$ ;r)  $\text{O-C}(=\text{O})\text{-R}^{14}$ ;s)  $\text{O-C}(=\text{O})\text{-NR}^{13}\text{R}^{13}$ ;

25

t)  $\text{O-C}(=\text{O})\text{-OR}^{15}$ ;u)  $\text{CN}$ ;

30

each  $\text{R}^{12}$  is independently H;  $\text{C}_1$  to  $\text{C}_6$  alkyl; benzyl; phenyl or substituted phenyl wherein the substituents are  $\text{C}_1$  to  $\text{C}_3$  alkyl, halogen, CN,  $\text{CF}_3$ ,  $\text{COOR}^{13}$ ,  $\text{C}_1$  to  $\text{C}_4$  perfluoroalkyl; or  $\text{CH}_2\text{COOR}^{13}$ ;



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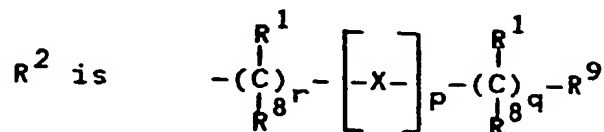
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each  $R^{13}$  is independently H, phenyl or  $C_1$  to  $C_6$  alkyl; and,

each  $R^{14}$  is independently H,  $(CH_2)_n COOR^{13}$  wherein n is 0 to 4,  $C_1$  to  $C_6$  alkyl,  $CF_3$ , phenyl, or substituted phenyl wherein substituted phenyl is as defined above in the definition of  $R^{12}$ ; or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

More preferred compositions of the present invention comprise compounds of the Formula I wherein:

$R^1$  is H or alkyl of 1 to 6 carbons or  $R^1$  and  $R^8$  taken together form a group  $(CH_2)_v$  wherein v is 1 to 7;



wherein:

each  $R^8$  is independently H, OH,  $C_1$  to  $C_4$ -O-alkyl or alkyl of 1 to 4 carbons; or an  $R^1$  and an  $R^8$  taken together form a group  $(CH_2)_v$  wherein v is 1 to 7;

$R^9$  is  $COOR^1$ ;  $CH_2OH$ ; CHO; tetrazole; hydroxymethylketone;

X is O; S;  $SO$ ;  $SO_2$ ;  $NR^{11}$  wherein  $R^{11}$  is H, alkyl of 1 to 6 carbons, acyl of 1 to 6 carbons, CN;  $CR^1R^8$ ;

or the unit  $\begin{array}{c} R^1 \quad R^8 \\ | \quad | \\ -C \cdots C- \end{array}$  wherein the dotted line represents an optional triple bond and in which the  $R^1$  and  $R^8$  substituents are absent when a triple bond is present;

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r and q are each independently 0 to 5 and p is 0 or 1 provided that the total of P, q and r is 2 to 4;

5  $R^3$  is H, alkyl of 1 to 6 carbons; phenyl or phenyl substituted by  $R^4$ ; or  $C_1$  to  $C_4$  alkyl-phenyl or  $C_1$  to  $C_4$  alkylphenyl in which the phenyl is substituted by  $R^4$ ;

$R^4$ ,  $R^5$ ,  $R^6$  and  $R^7$  are each independently selected from:

- 10 (1) hydrogen;
- (2) alkyl having 1 to 6 carbon atoms;
- (3) alkenyl having 2 to 6 carbon atoms;
- (4) M wherein M is
  - 15 a)  $OR^{12}$ ;
  - b) halogen;
  - c)  $CF_3$ ;
  - d)  $SR^{12}$ ;
  - e) phenyl or substituted phenyl
    - 20 wherein substituted phenyl is as defined below in the definition of  $R^{12}$ ;
    - f)  $COOR^{13}$ ;
    - 25 g)  $\begin{array}{c} O \\ || \\ C-R^{14} \end{array}$ ;
    - h) tetrazole;
    - i)  $-NH-\begin{array}{c} O \\ || \\ C-R^{15} \end{array}$  wherein  $R^{15}$  is
      - 30  $C_1$  to  $C_6$  alkyl, benzyl or phenyl;
      - j)  $-NR^{13}R^{13}$ ;

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k)  $-\text{NHSO}_2\text{R}^{16}$  wherein  $\text{R}^{16}$  is  $\text{C}_1$  to  $\text{C}_6$  alkyl, phenyl, or  $\text{CF}_3$ ;

5 l)  $-\overset{\text{O}}{\parallel}{\text{C}}-\text{CH}_2\text{OH}$ ;

m)  $-\text{SOR}^{12}$  wherein  $\text{R}^{12}$  is as defined above;

10 n)  $-\text{CONR}^{13}\text{R}^{13}$ ;

o)  $-\text{SO}_2\text{NR}^{13}\text{R}^{13}$ ;

p)  $-\text{SO}_2\text{R}^{12}$ ;

q)  $\text{NO}_2$ ;

15 r)  $-\overset{\text{O}}{\parallel}{\text{C}}-\text{R}^{14}$ ;

s)  $-\overset{\text{O}}{\parallel}{\text{C}}-\text{NR}^{13}\text{R}^{13}$ ;

t)  $-\overset{\text{O}}{\parallel}{\text{C}}-\text{OR}^{15}$ ;

u)  $\text{CN}$ ;

20 each  $\text{R}^{12}$  is independently H;  $\text{C}_1$  to  $\text{C}_6$  alkyl; benzyl; phenyl or substituted phenyl wherein the substituents are  $\text{C}_1$  to  $\text{C}_3$  alkyl, halogen, CN,  $\text{CF}_3$ ,  $\text{COOR}^{13}$ ,  $\text{CH}_2\text{COOR}^{13}$ , or  $\text{C}_1$  to  $\text{C}_4$  perfluoroalkyl;

25 each  $\text{R}^{13}$  is independently H, phenyl or  $\text{C}_1$  to  $\text{C}_6$  alkyl; and

30 each  $\text{R}^{14}$  is independently H,  $(\text{CH}_2)_n\text{COOR}^{13}$  wherein n is 0 to 4,  $\text{C}_1$  to  $\text{C}_6$  alkyl,  $\text{CF}_3$ , phenyl, or substituted phenyl wherein substituted phenyl is as defined above in the definition of  $\text{R}^{12}$ ; or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

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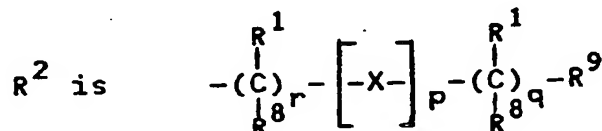
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Most preferred compositions of the present invention comprise compounds of the Formula I wherein:

$R^1$  is H or alkyl of 1 to 3 carbons or  $R^1$  and  $R^8$  taken together form a group  $(CH_2)_v$  wherein v is 1 to 7, with the proviso that  $R^1$  on the benzylic carbon attached to the indole nitrogen is H;



wherein:

each  $R^8$  is independently H, or alkyl of 1 to 4 carbons; or an  $R^1$  and an  $R^8$  taken together form a group  $(CH_2)_v$  wherein v is 1 to 7.

$R^9$  is  $COOR^1$ ;  $CH_2OH$ ;  $CHO$ ; or tetrazole;

X is O; S;  $SO$ ;  $SO_2$ ;  $NR^{11}$  wherein  $R^{11}$  is H, alkyl of 1 to 6 carbons, acyl of 1 to 6 carbons,  $CN$ ;  $CR^1R^8$ ;

or the unit  $\begin{array}{c} R^1 \quad R^8 \\ | \quad | \\ -C \equiv C- \end{array}$  wherein the dotted line represents an optional triple bond and in which the  $R^1$  and  $R^8$  substituents are absent when a triple bond is present;

r and q are each independently 0 to 5 and p is 0 or 1 provided that the total of p, q and r is 2 to 3;

$R^3$  is alkyl of 1 to 6 carbons, but is not cycloalkyl;

$R^4$ ,  $R^5$ ,  $R^6$  and  $R^7$  are each independently selected from:

(1) hydrogen;

(2) alkyl having 1 to 6 carbon atoms;

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(3) M wherein M is

a)  $\text{OR}^{12}$ ;

b) halogen;

c)  $\text{CF}_3$ ;

5

d)  $\text{SR}^{12}$ ;e)  $-\text{SOR}^{12}$ ;f)  $-\text{SO}_2\text{R}^{12}$ ;

10

g)  $\text{O}-\overset{\text{O}}{\parallel}{\text{C}}-\text{R}^{14}$  wherein  $\text{R}^{14}$  is H. $(\text{CH}_2)_n\text{COOR}^{13}$  wherein nis 0 to 4,  $\text{C}_1$  to  $\text{C}_6$ alkyl,  $\text{CF}_3$ , phenyl, or

substituted phenyl wherein

15

substituted phenyl is as

defined above in the

definition of  $\text{R}^{12}$ ; H,  $\text{C}_1$ to  $\text{C}_6$  alkyl,  $\text{CF}_3$ , phenyl

or substituted phenyl wherein

20

substituted phenyl is as

defined below in the

definition of  $\text{R}^{12}$ ;

h) CN;

each  $\text{R}^{12}$  is independently H;  $\text{C}_1$  to  $\text{C}_6$ 

25 alkyl; benzyl; phenyl or substituted phenyl wherein

the substituents are  $\text{C}_1$  to  $\text{C}_3$  alkyl, halogen, CN, $\text{CF}_3$ ,  $\text{COOR}^{13}$ ,  $\text{CH}_2\text{COOR}^{13}$ , wherein  $\text{R}^{13}$  is H,phenyl,  $\text{C}_1$  to  $\text{C}_6$  alkyl, or  $\text{C}_1$  to  $\text{C}_4$ 

perfluoroalkyl;

30 or a pharmaceutically acceptable salt thereof, and a  
pharmaceutically acceptable carrier.

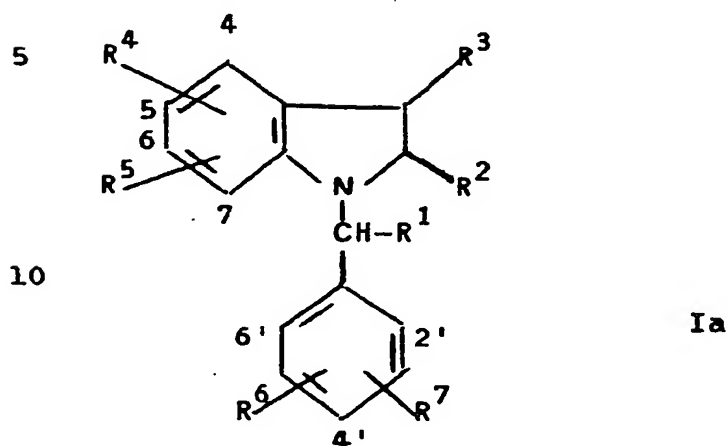
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The present invention also relates to novel compounds of Formula I represented by Formula Ia:



15

wherein:

$R^1$  is H or alkyl of 1 to 6 carbons or  $R^1$  and  $R^8$  taken together form a group  $(CH_2)_v$  wherein  $v$  is 1 to 7;

20

$R^2$  is  $-(C)_{r-}^{R^1} \left[ -X- \right]_p -(C)_{q-}^{R^1} - R^9$

wherein:

25 each  $R^8$  is independently H, OH,  $C_{11}$  to  $C_4$ -O-alkyl, or alkyl of 1 to 4 carbons or  $R^1$  and

$R^8$  taken together form a group  $(CH_2)_v$  wherein  $v$  is 1 to 7;

30  $R^9$  is  $COOR^1$ ;  $CH_2OH$ ;  $CHO$ ; tetrazole;  $NHSO_2R^{10}$  wherein  $R^{10}$  is OH, alkyl or alkoxy of 1 to 6 carbons, perhaloalkyl of 1 to 6 carbons, phenyl or phenyl substituted by alkyl or alkoxy

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groups of 1 to 3 carbons, halogen, hydroxy, COOH, CN, formyl or acyl to 1 to 6 carbons;  $\text{CONHSO}_2\text{R}^{10}$ ; hydroxymethylketone; CN; or  $\text{CON}(\text{R}^8)_2$ ;

5 X is O; S; SO;  $\text{SO}_2$ ;  $\text{NR}^{11}$  wherein  $\text{R}^{11}$  is H, alkyl of 1 to 6 carbons, acyl of 1 to 6 carbons, CN;  $\text{CR}^1\text{R}^8$ ;

or the unit  $\begin{array}{c} \text{R}^1 \quad \text{R}^8 \\ | \quad | \\ -\text{C} \equiv \text{C}- \end{array}$  wherein the dotted line represents an optional triple bond and in which the  $\text{R}^1$  and  $\text{R}^8$  substituents are absent when a triple bond is present;

r and q are each independently 0 to 5 and p is 0 or 1 provided that the total of p, q and r is 2 to 6, with the proviso that when  $\text{R}^1$  and  $\text{R}^8$  are H, X is  $\text{CH}_2$ ,  $\text{R}^4$  is 5-methoxy and  $\text{R}^6$  is halogen, then the sums of p, q and r is 3 to 6;

$\text{R}^3$  is H, alkyl of 1 to 6 carbons; phenyl or phenyl substituted by  $\text{R}^4$ ; or  $\text{C}_1$  to  $\text{C}_4$  alkyl-phenyl or  $\text{C}_1$  to  $\text{C}_4$  alkylphenyl in which the phenyl is substituted by  $\text{R}^4$ ;

$\text{R}^4$ ,  $\text{R}^5$ ,  $\text{R}^6$  and  $\text{R}^7$  are each independently selected from:

- (1) hydrogen;
- (2) alkyl having 1 to 6 carbon atoms;
- 25 (3) alkenyl having 2 to 6 carbon atoms;
- (4)  $-(\text{CH}_2)_n\text{M}$  wherein n is 0 to 3 and M is
  - a)  $\text{OR}^{12}$ ;
  - b) halogen;
  - 30 c)  $\text{CF}_3$ ;
  - d)  $\text{SR}^{12}$ ;

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- e) phenyl or substituted phenyl  
wherein substituted phenyl is  
as defined below in the  
definition of  $R^{12}$ ;
- 5 f)  $\text{COOR}^{13}$ ;
- g)  $\text{C}(=\text{O})\text{R}^{14}$ ;
- h) tetrazole;
- 10 i)  $-\text{NH}-\text{C}(=\text{O})\text{R}^{15}$  wherein  $R^{15}$  is  
 $\text{C}_1$  to  $\text{C}_6$  alkyl, benzyl or  
phenyl;
- j)  $-\text{NR}^{13}\text{R}^{13}$ ;
- 15 k)  $-\text{NHSO}_2\text{R}^{16}$  wherein  $R^{16}$   
is  $\text{C}_1$  to  $\text{C}_6$  alkyl,  
phenyl, or  $\text{CF}_3$ ;
- l)  $-\text{C}(=\text{O})\text{CH}_2\text{OH}$ ;
- 20 m)  $-\text{SOR}^{12}$ ;
- n)  $-\text{CONR}^{13}\text{R}^{13}$ ;
- o)  $-\text{SO}_2\text{NR}^{13}\text{R}^{13}$ ;
- p)  $-\text{SO}_2\text{R}^{12}$ ;
- q)  $\text{NO}_2$ ;
- 25 r)  $\text{O}-\text{C}(=\text{O})\text{R}^{14}$ ;
- s)  $\text{O}-\text{C}(=\text{O})\text{NR}^{13}\text{R}^{13}$ ;
- 30 t)  $\text{O}-\text{C}(=\text{O})\text{OR}^{15}$ ;
- u)  $\text{CN}$ ;



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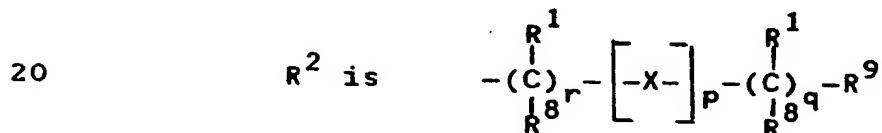
each  $R^{12}$  is independently H;  $C_1$  to  $C_6$  alkyl; benzyl; phenyl or substituted phenyl wherein the substituents are  $C_1$  to  $C_3$  alkyl, halogen, CN,  $CF_3$ ,  $COOR^{13}$ ,  $CH_2COOR^{13}$ ,  $C_1$  to  $C_3$  alkoxy, or  $C_1$  to  $C_4$  perfluoroalkyl;

each  $R^{13}$  is independently H, phenyl or  $C_1$  to  $C_6$  alkyl;

each  $R^{14}$  is independently H,  $(CH_2)_nCOOR^{13}$  wherein n is 0 to 4,  $C_1$  to  $C_6$  alkyl,  $CF_3$ , phenyl, or substituted phenyl wherein substituted phenyl is as defined above in the definition of  $R^{12}$ ; or a pharmaceutically acceptable salt thereof.

Preferred novel compounds of the present invention are compounds of the Formula Ia wherein:

$R^1$  is H or alkyl of 1 to 6 carbons or  $R^1$  and  $R^8$  taken together form a group  $(CH_2)_v$  wherein v is 1 to 7;



wherein:

each  $R^8$  is independently H, OH,  $C_1$  to  $C_4$ -O-alkyl, or alkyl of 1 to 4 carbons or  $R^1$  and

$R^8$  taken together form a group  $(CH_2)_v$  wherein v is 1 to 7;

$R^9$  is  $COOR^1$ ;  $CH_2OH$ ; CHO; tetrazole;  $CONHSO_2R^{10}$  wherein  $R^{10}$  is OH, alkyl or alkoxy of 1 to 6 carbons, perhaloalkyl of 1 to 6 carbons, phenyl or phenyl substituted by alkyl or alkoxy groups of 1 to 3 carbons, halogen, hydroxy, COOH, CN,

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formyl or acyl to 1 to 6 carbons; hydroxymethyl-  
ketone; CN; or  $\text{CON}(\text{R}^8)_2$ ;

5 X is O; S; SO;  $\text{SO}_2$ ;  $\text{NR}^{11}$  wherein  $\text{R}^{11}$   
is H, alkyl of 1 to 6 carbons, acyl of 1 to 6  
carbons, CN;  $\text{CR}^1\text{R}^8$ ;  
 $\text{R}^1\text{R}^8$

or the unit  $-\text{C}\equiv\text{C}-$  wherein the dotted line  
represents an optional triple bond and in which the  
 $\text{R}^1$  and  $\text{R}^8$  substituents are absent when a triple  
10 bond is present;

r and q are each independently 0 to 5 and p  
is 0 or 1 provided that the total of p, q and r is 2  
to 4, with the proviso that when  $\text{R}^1$  and  $\text{R}^8$  are H,  
X is  $\text{CH}_2$ ,  $\text{R}^4$  is 5-methoxy and  $\text{R}^6$  is halogen,  
15 then the sums of p, q and r is 3 to 4;

$\text{R}^3$  is H, alkyl of 1 to 6 carbons; phenyl  
or phenyl substituted by  $\text{R}^4$ ; or  $\text{C}_1$  to  $\text{C}_4$  alkyl-  
phenyl or  $\text{C}_1$  to  $\text{C}_4$  alkylphenyl in which the  
phenyl is substituted by  $\text{R}^4$ ;

20  $\text{R}^4$ ,  $\text{R}^5$ ,  $\text{R}^6$  and  $\text{R}^7$  are each  
independently selected from:

- (1) hydrogen;  
(2) alkyl having 1 to 6 carbon atoms;  
(3) alkenyl having 2 to 6 carbon atoms;  
25 (4)  $-(\text{CH}_2)_n\text{M}$

wherein n is 0 or 1 and M is

- a)  $\text{OR}^{12}$ ;  
b) halogen;  
c)  $\text{CF}_3$ ;  
30 d)  $\text{SR}^{12}$ ;

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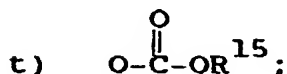
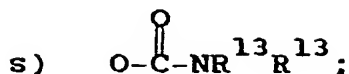
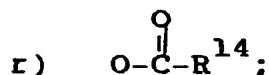
- e) phenyl or substituted phenyl wherein substituted phenyl is as defined below in the definition of  $R^{12}$ ;
- 5 f)  $\text{COOR}^{13}$ ;
- g)  $\text{C}(=\text{O})\text{-R}^{14}$  wherein  $R^{14}$  is H,  $(\text{CH}_2)_n\text{COOR}^{13}$  wherein n is 0 to 4,  $\text{C}_1$  to  $\text{C}_6$  alkyl,  $\text{CF}_3$ , phenyl, or substituted phenyl wherein substituted phenyl is as defined below in the definition of  $R^{12}$ ;
- 10 h) tetrazole;
- i)  $-\text{NH}-\text{C}(=\text{O})\text{-R}^{15}$  wherein  $R^{15}$  is  $\text{C}_1$  to  $\text{C}_6$  alkyl, benzyl or phenyl;
- 15 j)  $-\text{NR}^{13}\text{R}^{13}$ ;
- k)  $-\text{NHSO}_2\text{R}^{16}$  wherein  $R^{16}$  is  $\text{C}_1$  to  $\text{C}_6$  alkyl, phenyl, or  $\text{CF}_3$ ;
- 20 l)  $-\text{C}(=\text{O})\text{-CH}_2\text{OH}$ ;
- 25 m)  $-\text{SOR}^{12}$ ;
- n)  $-\text{CONR}^{13}\text{R}^{13}$ ;
- o)  $-\text{SO}_2\text{NR}^{13}\text{R}^{13}$ ;
- 30 p)  $-\text{SO}_2\text{R}^{12}$ ;
- q)  $\text{NO}_2$ ;

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each  $\text{R}^{12}$  is independently H;  $\text{C}_1$  to  $\text{C}_6$  alkyl; benzyl; phenyl or substituted phenyl wherein the substituents are  $\text{C}_1$  to  $\text{C}_3$  alkyl, halogen, CN,  $\text{CF}_3$ ,  $\text{COOR}^{13}$ ,  $\text{CH}_2\text{COOR}^{13}$   $\text{C}_1$  to  $\text{C}_3$  alkoxy  $\text{C}_1$  to  $\text{C}_4$  perfluoroalkyl;

10

each  $\text{R}^{13}$  is independently H, phenyl or  $\text{C}_1$  to  $\text{C}_6$  alkyl;

15

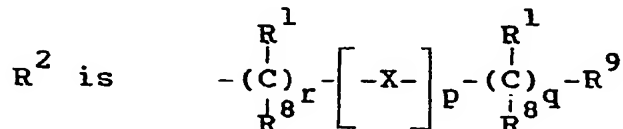
each  $\text{R}^{14}$  is independently H,  $(\text{CH}_2)_n\text{COOR}^{13}$  wherein n is 0 to 4,  $\text{C}_1$  to  $\text{C}_6$  alkyl,  $\text{CF}_3$ , phenyl, or substituted phenyl wherein substituted phenyl is as defined above in the definition of  $\text{R}^{12}$ ;

or a pharmaceutically acceptable salt thereof.

More preferred novel compounds of the present invention are compounds of the formula Ia wherein:

$\text{R}^1$  is H or alkyl of 1 to 6 carbons or  $\text{R}^1$  and  $\text{R}^8$  taken together form a group  $(\text{CH}_2)_v$  wherein v is 1 to 7;

25



30 wherein:

each  $\text{R}^8$  is independently H, OH,  $\text{C}_1$  to  $\text{C}_4$ -O-alkyl, or alkyl of 1 to 4 carbons or  $\text{R}^1$  and

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$R^8$  taken together form a group  $(CH_2)_v$  wherein  $v$  is 1 to 7;

$R^9$  is  $COOR^1$ ;  $CH_2OH$ ;  $CHO$ ; tetrazole; hydroxymethylketone;

5  $X$  is  $O$ ;  $S$ ;  $SO$ ;  $SO_2$ ;  $NR^{11}$  wherein  $R^{11}$  is  $H$ , alkyl of 1 to 6 carbons, acyl of 1 to 6 carbons,  $CN$ ;  $CR^1R^8$ ;

10 or the unit  $\begin{array}{c} R^1 \quad R^8 \\ | \quad | \\ -C \cdots C- \end{array}$  wherein the dotted line represents an optional triple bond and in which the  $R^1$  and  $R^8$  substituents are absent when a triple bond is present;

15  $r$  and  $q$  are each independently 0 to 5 and  $p$  is 0 or 1 provided that the total of  $p$ ,  $q$  and  $r$  is 2 to 4, with the proviso that when  $R^1$  and  $R^8$  are  $H$ ,  $X$  is  $CH_2$ ,  $R^4$  is 5-methoxy and  $R^6$  is halogen, then the sums of  $p$ ,  $q$  and  $r$  is 3 to 4;

20  $R^3$  is  $H$ , alkyl of 1 to 6 carbons; phenyl or phenyl substituted by  $R^4$ ; or  $C_1$  to  $C_4$  alkyl-phenyl or  $C_1$  to  $C_4$  alkylphenyl in which the phenyl is substituted by  $R^4$ ;

$R^4$ ,  $R^5$ ,  $R^6$  and  $R^7$  are each independently selected from:

- (1) hydrogen;
- 25 (2) alkyl having 1 to 6 carbon atoms;
- (3) alkenyl having 2 to 6 carbon atoms;
- (4)  $M$  wherein  $M$  is
  - a)  $OR^{12}$ ;
  - b) halogen;
  - 30 c)  $CF_3$ ;

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- d)  $SR^{12}$ ;  
 e) phenyl or substituted phenyl  
 wherein substituted phenyl is  
 as defined below in the  
 definition of  $R^{12}$ ;

10

- f)  $COOR^{13}$ ;  

$$\begin{array}{c} O \\ || \\ C-R^{14} \end{array}$$
  
 g)  $C-R^{14}$ ;  
 h) tetrazole;

15

- i)  $-NH-C(=O)-R^{15}$  wherein  $R^{15}$  is  
 $C_1$  to  $C_6$  alkyl, benzyl or  
 phenyl;  
 j)  $-NR^{13}R^{13}$ ;  
 k)  $-NHSO_2R^{16}$  wherein  $R^{16}$   
 is  $C_1$  to  $C_6$  alkyl,  
 phenyl, or  $CF_3$ ;

20

- l) 
$$\begin{array}{c} O \\ || \\ -C-CH_2OH \end{array}$$
;  
 m)  $-SOR^{12}$ ;  
 n)  $-CONR^{13}R^{13}$ ;  
 o)  $-SO_2NR^{13}R^{13}$ ;  
 p)  $-SO_2R^{12}$ ;  
 q)  $NO_2$ ;

25

- r) 
$$\begin{array}{c} O \\ || \\ O-C-R^{14} \end{array}$$
;  
 s) 
$$\begin{array}{c} O \\ || \\ O-C-NR^{13}R^{13} \end{array}$$
;  
 t) 
$$\begin{array}{c} O \\ || \\ O-C-OR^{15} \end{array}$$
;  
 u)  $CN$ ;

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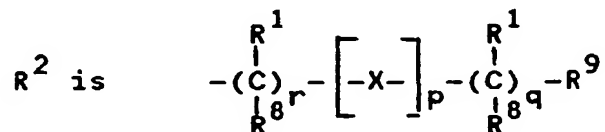
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- each  $R^{12}$  is independently H;  $C_1$  to  $C_6$  alkyl; benzyl; phenyl or substituted phenyl wherein the substituents are  $C_1$  to  $C_3$  alkyl, halogen, CN,  $CF_3$ ,  $COOR^{13}$ ,  $CH_2COOR^{13}$ ,  $C_1$  to  $C_3$  alkoxy or
- 5  $C_1$  to  $C_4$  perfluoroalkyl;
- each  $R^{13}$  is independently H, phenyl or  $C_1$  to  $C_6$  alkyl; and
- each  $R^{14}$  is H,  $(CH_2)_nCOOR^{13}$  wherein  $n$  is 0 to 4,  $C_1$  to  $C_6$  alkyl,  $CF_3$ , phenyl, or
- 10 substituted phenyl wherein substituted phenyl is as defined above in the definition of  $R^{12}$ ;
- or a pharmaceutically acceptable salt thereof.

- Most preferred novel compounds of the
- 15 present invention are compounds of the formula Ia wherein:

- $R^1$  is H or alkyl of 1 to 3 carbons or  $R^1$  and  $R^8$  taken together form a group  $(CH_2)_v$  wherein  $v$  is 1 to 7, with the proviso that  $R^1$  on
- 20 the benzylic carbon attached to the indole nitrogen is H;



- 25 wherein:

- each  $R^8$  is independently H, OH,  $C_1$  to  $C_4$ -O-alkyl or alkyl of 1 to 4 carbons or  $R^1$  and
- $R^8$  taken together form a group  $(CH_2)_v$  wherein  $v$
- 30 is 1 to 7;
- $R^9$  is  $COOR^1$ ;  $CH_2OH$ ; CHO; or tetrazole;

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X is O; S; SO; SO<sub>2</sub>; NR<sup>11</sup> wherein R<sup>11</sup> is H, alkyl of 1 to 6 carbons, acyl of 1 to 6 carbons. CN; CR<sup>1</sup>R<sup>8</sup>;

5 or the unit  $\begin{array}{c} \text{R}^1 \quad \text{R}^8 \\ | \quad | \\ -\text{C} \equiv \text{C}- \end{array}$  wherein the dotted line represents an optional triple bond and in which the R<sup>1</sup> and R<sup>8</sup> substituents are absent when a triple bond is present;

10 r and q are each independently 0 to 5 and p is 0 or 1 provided that the total of p, q and r is 2 to 3, with the proviso that when R<sup>1</sup> and R<sup>8</sup> are H, X is CH<sub>2</sub>, R<sup>4</sup> is 5-methoxy and R<sup>6</sup> is halogen, then the sum of r, p and q is 3 to 4;

15 R<sup>3</sup> is alkyl of 1 to 6 carbons, but not cycloalkyl;

R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup> and R<sup>7</sup> are each independently selected from:

- (1) hydrogen;
- (2) alkyl having 1 to 6 carbon atoms;
- 20 (3) M wherein M is

- a) OR<sup>12</sup>;
- b) halogen;
- c) CF<sub>3</sub>;
- 25 d) SR<sup>12</sup>;
- e) -SOR<sup>12</sup>;
- f) -SO<sub>2</sub>R<sup>12</sup>;

- 30 g)  $\text{O} \parallel \text{C}-\text{R}^{14}$ , wherein R<sup>14</sup> is H, C<sub>1</sub> to C<sub>6</sub> alkyl, CF<sub>3</sub>, phenyl or substituted phenyl wherein substituted phenyl is



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as defined below in the  
definition of  $R^{12}$ ;

h) CN;

each  $R^{12}$  is independently H;  $C_1$  to  $C_6$   
alkyl; benzyl; phenyl or substituted phenyl wherein  
the substituents are  $C_1$  to  $C_3$  alkyl, halogen, CN,  
 $CF_3$ ,  $COOR^{13}$ ,  $CH_2COOR^{13}$ ,  $C_1$  to  $C_3$  alkoxy;  
or  $C_1$  to  $C_4$  perfluoroalkyl;

each  $R^{13}$  is independently H, phenyl or  
 $C_1$  to  $C_6$  alkyl;  
or a pharmaceutically acceptable salt thereof.

Most-particularly preferred novel compounds  
of the present invention are compounds of the formula  
Ia wherein:

$R^1$  is H or alkyl of 1 to 3 carbons, with  
the proviso that  $R^1$  on the benzylic carbon attached  
to the indole nitrogen is H;

$R^2$  is

$$-(\overset{\overset{R^1}{|}}{\underset{\underset{R^8}{|}}{C}})_r - [-X-]_p - (\overset{\overset{R^1}{|}}{\underset{\underset{R^8}{|}}{C}})_q - R^9$$

wherein:

each  $R^8$  is independently H or alkyl of 1  
to 4 carbons, with the proviso that at least one of  
the  $R^1$  or  $R^8$  substituents in  $R^2$  is not hydrogen;

$R^9$  is  $COOH$ ;  $CH_2OH$ ;  $CHO$ ; or tetrazole;

X is  $CR^1R^8$ ;

r and q are each independently 0 to 3 and p  
is 0 or 1 provided that the total of p, q and r is 2  
to 3;

$R^3$  is alkyl of 1 to 6 carbons, but not  
cycloalkyl;

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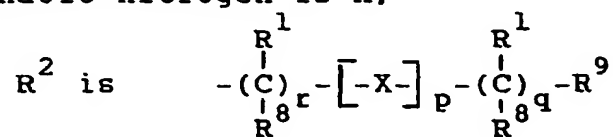
$R^4$ ,  $R^5$ ,  $R^6$  and  $R^7$  are each independently selected from:

- (1) hydrogen;
- (2) alkyl having 1 to 6 carbon atoms;
- 5 (3) M wherein M is
  - a)  $OR^{12}$ ;
  - b) halogen;
  - c)  $CF_3$ ;
  - 10 d)  $SR^{12}$ ;
  - e)  $-SOR^{12}$ ;
  - f)  $-SO_2R^{12}$ ;
  - 15 g)  $O-\overset{\overset{O}{\parallel}}{C}-R^{14}$ , wherein  $R^{14}$  is H,  $C_1$  to  $C_6$  alkyl,  $CF_3$ , phenyl or substituted phenyl wherein substituted phenyl is as defined below in the definition of  $R^{12}$ ;
  - 20 h) CN;

each  $R^{12}$  is independently H;  $C_1$  to  $C_6$  alkyl; or benzyl; or a pharmaceutically acceptable salt thereof.

25 Other most-particularly preferred novel compounds of the present invention are compounds of the formula Ia wherein:

$R^1$  is H or alkyl of 1 to 3 carbons, with the proviso that  $R^1$  on the benzylic carbon attached  
30 to the indole nitrogen is H;



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wherein:

each  $R^8$  is independently H or alkyl of 1 to 4 carbons;

$R^9$  is COOH;  $CH_2OH$ ; CHO; or tetrazole;

5 X is O; S; SO; or  $SO_2$ ;

r and q are each independently 0 to 3 and p is 1 provided that the total of p, q and r is 2 to 3;

$R^3$  is alkyl of 1 to 6 carbons, but not cycloalkyl;

10  $R^4$ ,  $R^5$ ,  $R^6$  and  $R^7$  are each independently selected from:

(1) hydrogen;

(2) alkyl having 1 to 6 carbon atoms;

(3) M wherein M is

15 a)  $OR^{12}$ ;

b) halogen;

c)  $CF_3$ ;

d)  $SR^{12}$ ;

20 e)  $-SOR^{12}$ ;

f)  $-SO_2R^{12}$ ;

g)  $O-\overset{\overset{O}{\parallel}}{C}-R^{14}$ , wherein  $R^{14}$  is H,

25  $C_1$  to  $C_6$  alkyl,  $CF_3$ , phenyl or substituted phenyl wherein substituted phenyl is as defined below in the definition of  $R^{12}$ ;

h) CN;

30 each  $R^{12}$  is independently H;  $C_1$  to  $C_6$  alkyl; or benzyl;

or a pharmaceutically acceptable salt thereof.

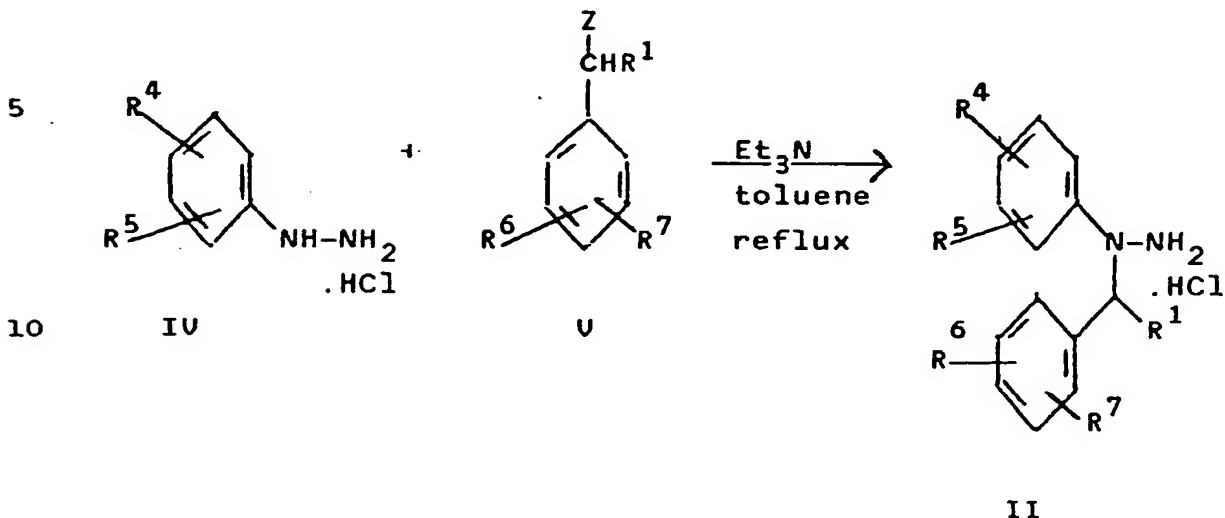


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Scheme II      Preparation of Hydrazine Derivatives (II)

15

With regard to Scheme I, the alkanol solvent can have an important effect on the course of the reaction. With some of the ketones III, the final product may contain a mixture of the isomers I and Ib. Formation of the undesired Ib is minimized by using isopropanol or tert-butanol in place of methanol or ethanol.

The sequence described above is an application of the Fischer Indole Synthesis.

25 Numerous indole syntheses are described in reviews, such as, for example "Heterocyclic Compounds" Volume 25, Parts I, II, III, W. J. Houlihan (Ed.), Interscience, J. Wiley & Sons, N. Y., 1979.

Appropriate manipulations of functional groups using sequences described in such reviews will lead to the compounds of the present invention. Another useful

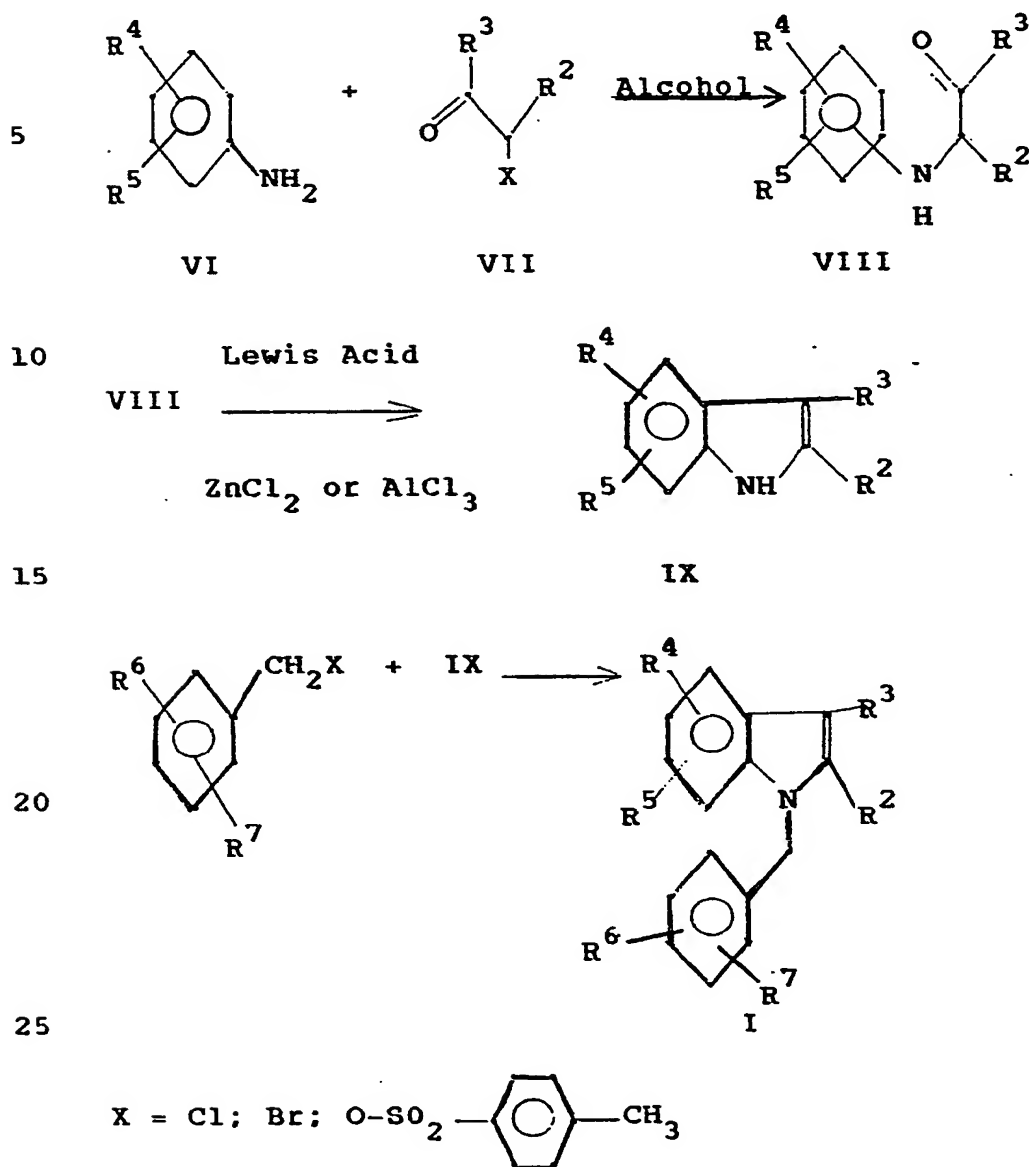
30 sequence is shown in Scheme III.

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Scheme III      Preparation of Indole-2-Alkanoic acids

30

The Bischler Indole Synthesis used in the sequence described for the synthesis of compounds of the present invention envisages the alkylation of an

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appropriately substituted halo or tosyloxy ketone  
(VII) by an appropriately substituted aniline  
derivative (VI), in an alcoholic solvent. The  
condensation step is effected through the use of a  
5 Lewis Acid or mineral acid. The indole derivative so  
produced (IX) may then be alkylated by an  
aralkylhalide to product I.

The following ketones (1-7) of structure III  
10 are known in the art:

15

20

25

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TABLE 1Ketones of Formula III

5	<u>No.</u>	<u>Structure</u>	<u>Reference</u>
	1.		Methyl 4-oxohexanoate: B. L. Feringa and W. Dannenberg, Synth. Commun., <u>13</u> , 509-514 (1983).
10			
15	2.		Ethyl 4-oxohexanoate: D. A. Wehrli and V. Chu, Org. Synth., <u>58</u> , 79-82 (1978).
20	3.		3-Methyl-4-oxohexanoate: A. P. Cowling and J. Mann, J. Chem. Soc., Chem. Commun., 1006-1007 (1978).
25	4.		Methyl 2,2-dimethyl-4-oxohexanoate: R. Scarpati, G. Scherillo, F. Imperato and R. A. Nicolaus, Gazz. Chim. Ital., <u>97</u> , 654-664 (1967).
30			
	5.		Methyl 5-oxoheptanoate: M. K. Eberle and G. G. Kahle, Tetrahedron Lett., <u>21</u> , 2303-2304 (1980).

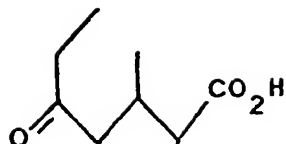


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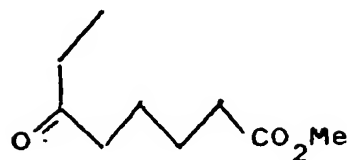
6.



3-Methyl-5-oxoheptanoic  
acid: C. Conti,  
A. Niccoli and R. Rossi,  
Chim. Ind. (Milan) 58: 877  
(1976).

5

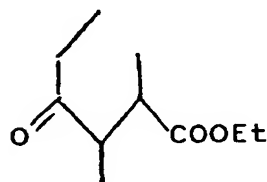
7.



Methyl 6-oxooctanoate:  
T. Terasawa and T. Okada,  
Tetrahedron 33, 595-598  
(1977).

10

8.



Ethyl 2,3-dimethyl-4-oxo-  
hexanoate

15

Examples of Formula I compounds useful in  
the pharmaceutical compositions of the present  
invention are tabulated below. The numbers preceding  
the  $R^4$ ,  $R^5$ ,  $R^6$ , and  $R^7$  definitions indicate  
the substituent position in the structure. Standard  
abbreviations such as Me for methyl, Et for ethyl, Pr  
for propyl, Bu for butyl, Ac for acetyl, and Ph for  
phenyl are used. Compounds 3 to 72 are novel  
compounds.

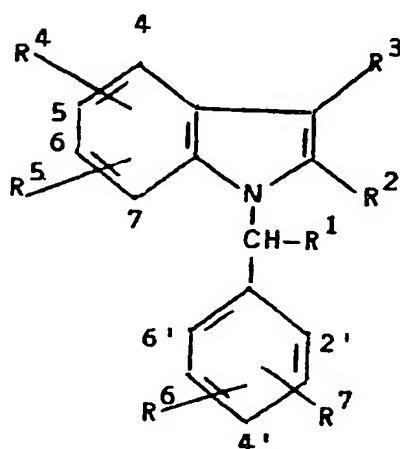
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TABLE 2Compounds of the Formula I

I

Compound		R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>	R <sup>6</sup>	R <sup>7</sup>
No.								
20	1	H	(CH <sub>2</sub> ) <sub>2</sub> CO <sub>2</sub> H	Me	5-OMe	H	4'-Cl	H
	2	H	(CH <sub>2</sub> ) <sub>2</sub> CO <sub>2</sub> Me	Me	5-OMe	H	4'-Cl	H
	3	H	(CH <sub>2</sub> ) <sub>2</sub> CO <sub>2</sub> H	Me	5-F	H	4'-Cl	H
	4	H	(CH <sub>2</sub> ) <sub>2</sub> CO <sub>2</sub> H	Me	4-Cl	6-Cl	4'-Cl	H
	5	H	(CH <sub>2</sub> ) <sub>2</sub> CO <sub>2</sub> H	Me	4-OMe	H	4'-Cl	H
25	6	H	(CH <sub>2</sub> ) <sub>2</sub> CO <sub>2</sub> H	Me	6-OMe	H	4'-Cl	H
	7	H	(CH <sub>2</sub> ) <sub>2</sub> CO <sub>2</sub> H	Me	4-Me	H	4'-Cl	H
	8	H	(CH <sub>2</sub> ) <sub>2</sub> CO <sub>2</sub> H	Me	6-Me	H	4'-Cl	H
	9	H	(CH <sub>2</sub> ) <sub>4</sub> CO <sub>2</sub> H	Me	5-OMe	H	4'-Cl	H
	10	H	(CH <sub>2</sub> ) <sub>2</sub> CO <sub>2</sub> H	Me	5-Me	H	4'-Cl	H
30	11	H	(CH <sub>2</sub> ) <sub>3</sub> CO <sub>2</sub> H	Me	5-OMe	H	4'-Cl	H
	12	H	(CH <sub>2</sub> ) <sub>2</sub> CO <sub>2</sub> H	Me	5-OH	H	4'-Cl	H
	13	H	(CH <sub>2</sub> ) <sub>2</sub> CO <sub>2</sub> H	Me	5-Cl	H	4'-Cl	H

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Compound								
No.		R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>	R <sup>6</sup>	R <sup>7</sup>
14	H	(CH <sub>2</sub> ) <sub>2</sub>	CO <sub>2</sub> H	Me	H	H	4'-Cl	H
15	H	(CH <sub>2</sub> ) <sub>2</sub>	CO <sub>2</sub> H	Me	5-Br	H	4'-Cl	H
5								
16	H	(CH <sub>2</sub> ) <sub>2</sub>	CO <sub>2</sub> H	Me	5-OMe	H	4'-S(=O)-Me	H
17	H	(CH <sub>2</sub> ) <sub>2</sub>	CO <sub>2</sub> H	Me	5-OMe	H	4'-SMe	H
18	H	(CH <sub>2</sub> ) <sub>3</sub>	CO <sub>2</sub> H	Me	5-OMe	H	4'-SMe	H
19	H	(CH <sub>2</sub> ) <sub>3</sub>	CO <sub>2</sub> H	Me	5-F	H	4'-Cl	H
10	20	H	(CH <sub>2</sub> ) <sub>2</sub>	CO <sub>2</sub> H	Me	5-F	4'SMe	H
21	H	(CH <sub>2</sub> ) <sub>2</sub>	CO <sub>2</sub> H	Me	5-F	H	4'-S(=O)-Me	H
22	H	CH(Me)CH <sub>2</sub>	CO <sub>2</sub> H	Me	5-OMe	H	4'-Cl	H
23	H	CH <sub>2</sub> OCH <sub>2</sub>	CO <sub>2</sub> H	Me	5-OMe	H	4'-Cl	H
15	24	H	(CH <sub>2</sub> ) <sub>2</sub>	CO <sub>2</sub> H	Me	5-OAc	4'-Cl	H
25	25	H	CH <sub>2</sub> CH(Me)CH <sub>2</sub>	CO <sub>2</sub> H	Me	5-OMe	4'-Cl	H
26	H	(CH <sub>2</sub> )CH(Me)CH <sub>2</sub>	CO <sub>2</sub> H	H	5-F	H	4'-Cl	H
27	H	CH <sub>2</sub> C(Me) <sub>2</sub>	CO <sub>2</sub> H	H	5-OMe	H	4'-Cl	H
28	H	(CH <sub>2</sub> ) <sub>3</sub>	CO <sub>2</sub> H	Me	5-F	H	4'-SMe	H
20	29	H	(CH <sub>2</sub> ) <sub>2</sub>	CO <sub>2</sub> H	Me	5-OMe	H	H
30	H	(CH <sub>2</sub> ) <sub>2</sub>	CO <sub>2</sub> H	Me	H	H	H	H
31	H	(CH <sub>2</sub> ) <sub>2</sub>	CO <sub>2</sub> H	Me	5-OMe	H	4'-CF <sub>3</sub>	H
32	H	(CH <sub>2</sub> ) <sub>2</sub>	CO <sub>2</sub> H	Me	5-OMe	H	4-SMe	H
33	H	(CH <sub>2</sub> ) <sub>2</sub>	CO <sub>2</sub> H	Me	5-OMe	H	4-SMe	H
25								
34	H	(CH <sub>2</sub> ) <sub>2</sub>	CO <sub>2</sub> H	Me	5-OMe	H	4'-S(=O)-Me	H
35	H	(CH <sub>2</sub> ) <sub>2</sub>	CO <sub>2</sub> H	Me	5-F	H	4'-Cl	H
36	H	(CH <sub>2</sub> ) <sub>2</sub>	CO <sub>2</sub> H	Me	5-Cl	H	4'-Cl	H
30	37	H	(CH <sub>2</sub> ) <sub>2</sub>	CO <sub>2</sub> H	Me	5-Br	4'-Cl	H
38	Me	(CH <sub>2</sub> ) <sub>2</sub>	CO <sub>2</sub> H	Me	5-OMe	H	4'-Cl	H
39	H	(CH <sub>2</sub> ) <sub>2</sub>	CO <sub>2</sub> H	Et	5-OMe	H	4'-Cl	H

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	40	H	$(\text{CH}_2)_2\text{CO}_2\text{H}$	Me	5-OH	H	4'-Cl	H
	41	H	$(\text{CH}_2)_2\text{CO}_2\text{H}$	Me	5-OAc	H	4'-Cl	H
	42	H	$(\text{CH}_2)_2\text{CO}_2\text{H}$	Me	4-OMe	H	4'-Cl	H
	43	H	$(\text{CH}_2)_2\text{CO}_2\text{H}$	Me	4-Cl	H	4'-Cl	H
5	44	H	$(\text{CH}_2)_2\text{CO}_2\text{H}$	Me	4-Cl	6-Cl	4'-CF <sub>3</sub>	H
	45	H	$(\text{CH}_2)_3\text{CO}_2\text{H}$	Me	5-OMe	4-Cl	H	H
	46	same as 2 to 16 with R <sup>2</sup> being $(\text{CH}_2)_3\text{COOH}$						
	47	H	$\text{CH}(\text{Me})\text{CH}_2\text{CO}_2\text{H}$	Me	5-OMe	4-Cl	H	H
	48	same as 2 to 16 with R <sup>2</sup> being $\text{CH}(\text{Me})\text{CH}_2\text{COOH}$						
10	49	H	$\text{CH}_2-\text{CH}(\text{Me})-\text{COOH}$	Me	5-OMe	H	4'-Cl	H
	50	same as 2 to 16 with R <sup>2</sup> being $\text{CH}_2-\text{CH}(\text{Me})\text{COOH}$						
	51	H	$\text{CH}(\text{Me})(\text{CH}_2)_2-\text{COOH}$	Me	5-OMe	H	4'-Cl	H
	52	same as 2 to 16 with R <sup>2</sup> being $\text{CH}(\text{Me})(\text{CH}_2)_2-\text{COOH}$						
	53	H	$\text{CH}_2-\text{CH}(\text{Me})\text{CH}_2\text{COOH}$	Me	5-OMe	H	4'-Cl	H
15	54	same as 2 to 16 with R <sup>2</sup> being $\text{CH}_2-\underset{\text{Me}}{\text{CH}}-\text{CH}_2-\text{COOH}$						
	55	H	$\text{CH}_2\text{CH}_2\text{CH}(\text{Me})-\text{COOH}$	Me	5-OMe	H	4'-Cl	H
	56	same as 2 to 16 with R <sup>2</sup> being $(\text{CH}_2)_2-\text{CH}(\text{Me})\text{COOH}$						
	57	H	$\text{CH}_2-\text{C}(\text{Me})_2-\text{COOH}$	Me	5-OMe	H	4'-Cl	H
20	58	same as 2 to 16 with R <sup>2</sup> being $\text{CH}_2-\text{C}(\text{Me})_2-\text{COOH}$						
	59	H	$\text{CH}_2-\text{C}(\text{Me})_2\text{CH}_2\text{COOH}$	Me	5-OMe	H	4'Cl	H
	60	same as 2 to 16 with R <sup>2</sup> being $\text{CH}_2-\text{C}(\text{Me})_2-\text{CH}_2-\text{COOH}$						
	61	H	$(\text{CH}_2)_2-\text{C}(\text{Me})_2-\text{COOH}$	Me	5-OMe	H	4'Cl	H
25	62	same as 2 to 16 with R <sup>2</sup> being $(\text{CH}_2)_2-\text{C}(\text{Me})_2-\text{COOH}$						
	63	H	$\text{CH}_2-\text{OCH}_2\text{COOH}$	Me	5-OMe	H	4'Cl	H
	64	same as 2 to 16 with R <sup>2</sup> being $\text{CH}_2-\text{OCH}_2\text{COOH}$						
	65	H	$\text{CH}_2-\text{S}-\text{CH}_2\text{CO}_2\text{H}$	Me	5-OMe	H	4'Cl	H
	66	H	$\text{CH}_2-\underset{\text{O}}{\text{S}}-\text{CH}_2\text{CO}_2\text{H}$	Me	5-OMe	H	4'Cl	H

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	67	H	$\begin{array}{c} \text{O} \\ \parallel \\ \text{CH}_2\text{S}-\text{CH}_2\text{CO}_2\text{H} \\ \downarrow \\ \text{O} \end{array}$	Me	5-OMe	H	4'Cl	H
	68	same as 2 to 16 with $\text{R}^2$ being $\text{CH}_2\text{-S-CH}_2\text{CO}_2\text{H}$						
5	69	same as 2 to 16 with $\text{R}^2$ being $\text{CH}_2\text{-S-CH}_2\text{CO}_2\text{H}$						
	70	H	$\begin{array}{c} \text{C}(\text{CH}_3)_2\text{CH}_2\text{CO}_2\text{H} \\ \parallel \\ \text{CN} \end{array}$	Me	5-OMe	H	4'Cl	H
	71	H	$\begin{array}{c} \text{CH}_2\text{N-CHCH}_2\text{CO}_2\text{H} \\ \parallel \\ \text{CN} \end{array}$	Me	5-OMe	H	4'Cl	H
10	72	same as 2 to 16 with $\text{R}^2$ being $\text{CH}_2\text{-N-CH}_2\text{CO}_2\text{H}$						
	73	same as 2 to 16 with $\text{R}^2$ being $\text{CH}(\text{CH}_3)_2\text{COOH}$						
	74	same as 2 to 16 with $\text{R}^2$ being $\text{CH}(\text{CH}_3)\text{C}(\text{CH}_3)_2\text{CH}_2\text{COOH}$						

15

20

25

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Specific Examples of the Formula I compounds  
are the following, all but the first being novel:

5        3-[1-(4-chlorobenzyl)-3-methyl-5-methoxyindol-2-yl]  
         propionic acid;

         3-[1-(4-chlorobenzyl)-3-methyl-5-fluoroindol-2-yl]  
         propionic acid;

10       3-[1-(4-chlorobenzyl)-3,4-dimethylindol-2-yl]  
         propionic acid;

         4-[1-(4-chlorobenzyl)-3-methyl-5-methoxyindol-2-yl]  
         butanoic acid;  
15

         3-[1-(4-chlorobenzyl)-3-methyl-5-hydroxyindol-2-yl]  
         propionic acid;

20       3-[1-(4-chlorobenzyl)-3-methylindol-2-yl]propionic  
         acid;

         3-[1-(4-methylthiobenzyl)-3-methyl-5-methoxyindol-2-  
         yl]propionic acid;

25       3-[1-(4-methylthiobenzyl)-3-methyl-5-fluoroindol-2-yl]  
         propionic acid;

         3-[1-(4-methylsulfinylbenzyl)-3-methyl-5-methoxyindol-  
         2-yl]propionic acid;  
30

         4-[1-(4-methylthiobenzyl)-3-methyl-5-methoxyindol-  
         2-yl]butanoic acid;

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4-[1-(4-chlorobenzyl)-3-methyl-5-fluoroindol-2-yl]  
butanoic acid;

5 1-[1-(4-chlorobenzyl)-3-methyl-5-methoxyindol-2-yl]  
methoxy acetic acid;

3-[1-(4-chlorobenzyl)-3-methyl-5-methoxyindol-2-yl]-  
2,2-dimethylpropanoic acid;

10 3-[1-(4-chlorobenzyl)-3-methyl-5-methoxyindol-2-  
yl]-3-methylpropanoic acid;

3-methyl-4-[1-(4-chlorobenzyl)-5-methoxy-3-methyl-  
indol-2-yl]butanoic acid;

15 3-methyl-4-[1-(4-chlorobenzyl)-5-fluoro-3-methyl-  
indol-2-yl]butanoic acid;

20 3-[1-(4-chlorobenzyl-3-methyl-5-fluoro-2-indolyl)-2,2-  
dimethyl propanoic acid.

Further examples include:

25 4-[1-(4-chlorobenzyl-5-fluoro-3-methyl-1H-indol-2-yl)]-  
2,4,3,3-tetramethyl butanoic acid;

4-[1-(4-chlorobenzyl-5-fluoro-3-methyl-1H-indol-2-yl)]-  
4,3,3-trimethyl butanoic acid;

30 4-[1-(4-chlorobenzyl-5-fluoro-3-methyl-1H-indol-2-yl)]-  
2,2,3-trimethyl butanoic acid;

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- 4-[1-(4-chlorobenzyl-5-fluoro-3-methyl-1H-indol-2-yl)-  
2,3,3-trimethyl butanoic acid;
- 5 4-[1-(4-chlorobenzyl-5-methoxy-3-methyl-1H-indol-2-yl)-  
2,2,3-trimethyl butanoic acid;
- 4-[1-(4-chlorobenzyl-5-ethoxy-3-methyl-1H-indol-2-yl)-  
2,2,3-trimethyl butanoic acid;
- 10 4-[1-(4-chlorobenzyl-5-chloro-3-methyl-1H-indol-2-yl)-  
2,2,3-trimethyl butanoic acid;
- 4-[1-(4-chlorobenzyl-3-methyl-5-trifluoromethyl-1H-  
indol-2-yl)-2,4,3,3-tetramethyl butanoic acid;
- 15 4-[1-(4-chlorobenzyl-3-methyl-5-trifluoromethylthio-  
1H-indol-2-yl)-2,4,3,3-tetramethyl butanoic acid;
- 3-[1-(4-chlorobenzyl)-5-ethoxy-3-methyl-1H-indol-2-yl]-  
20 2,2,3-trimethyl propanoic acid;
- 3-[1-(4-chlorobenzyl)-5-ethoxy-3-methyl-1H-indol-2-yl]-  
2,3,3-trimethyl propanoic acid;
- 25 3-[1-(4-chlorobenzyl)-5-ethoxy-3-methyl-1H-indol-2-yl]-  
2,2,3,3-tetramethyl propanoic acid;
- 3-[1-(4-chlorobenzyl)-5-methoxy-3-methyl-1H-indol-2-  
yl]-2,2,3-trimethyl propanoic acid;
- 30 3-[1-(4-chlorobenzyl)-5-fluoro-3-methyl-1H-indol-2-  
yl]-2,2,3-trimethyl propanoic acid;



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3-[1-(4-chlorobenzyl)-5-chloro-3-methyl-1H-indol-2-yl]-2,2,3-trimethyl propanoic acid;

5 3-(1-p-chlorobenzyl-3-methyl-5-methoxyindol-2-yl)-2,2-diethyl propanoic acid;

3-[1-(4-chlorobenzyl)-3-methyl-5-fluoroindol-2-yl]-2,2-diethyl propanoic acid;

10 3-[1-(4-chlorobenzyl)-3-methyl-5-fluoroindol-2-yl]-2-ethyl propanoic acid;

15 3-[1-(4-chlorobenzyl)-3-ethyl-5-fluoroindol-2-yl]-3-methyl propanoic acid; and

3-[1-(4-chlorobenzyl-3-methyl-5-methoxy-2-indolyl)] pentanoic acid.

20 In those instances when asymmetric centers are present, more than one stereoisomer is possible, and all possible isomeric forms are deemed to be included within the planar structural representations shown. Optically active (R) and (S) isomers may be resolved using conventional techniques known to the  
25 skilled artisan.

The prostaglandin antagonist properties of the compounds of the present invention can be demonstrated by a number of biological assays, one of which, inhibition of platelet aggregation, is  
30 described below.

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### Inhibition of Induced Threshold Aggregation of Human Platelets

Human platelet rich plasma (PRP) is prepared from venous blood of male volunteers who have taken  
5 no medication for ten days prior to test. Blood is transferred into plastic centrifuge tubes containing 3.8% Trisodium Citrate in 0.9% NaCl (in a ratio of blood to anticoagulant of 9:1), mixed by gentle inversion, and centrifuged at room temperature for  
10 ten minutes at 116 g. The supernatant (PRP) is transferred into plastic tubes. Platelet poor plasma (PPP) is obtained by centrifuging the residual blood cells at 4000 g for ten minutes. PRP is left to stand at least one half hour prior to testing.

15 Platelet Aggregation is measured using a Payton Aggregometer and Recorder. Following calibration of the instrument, a cuvette containing PRP (225 microliters) is incubated for three minutes at 37°C. Drug vehicle (control), or a drug concentra-  
20 tion is then added in a volume of 0.5 microliter. After one minute, the aggregating agent (U44069, 9,11-dideoxy-9 $\alpha$ ,11 $\alpha$ -epoxymethano PGF<sub>2</sub>) is added to the cuvette in a volume of 25 microliters. Recording is continued until the maximal response is obtained.

25 The threshold (approximately 20 - 30% of maximum) aggregation concentration of the agonist to be used is first determined in the presence of the drug vehicle (control). Test compounds are then assayed at 10 or 30 micrograms/ml initially, and if  
30 active, are further tested in order to determine the concentration range at which 20-80% of the threshold aggregatory response is inhibited. All drugs are dissolved in dimethylsulfoxide.

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The height of the aggregation response (measured in divisions of the recorder paper, 1 division = 2.5 mm) in the presence of the drug is recorded, and calculated as percent inhibition of the mean height of the control threshold responses. The  $IC_{50}$  (drug concentration which inhibits 50% of the aggregatory response) is obtained by regression analysis.

Compounds of Formula I or Ia can be tested using the following assay to determine their mammalian leukotriene biosynthesis inhibiting activity.

Rat Peritoneal Polymorphonuclear (PMN)  
Leukocyte Assay

Rats under ether anesthesia are injected (i.p.) with 8 ml of a suspension of sodium caseinate (6 grams in ca. 50 ml water). After 15-24 hr. the rats are sacrificed ( $CO_2$ ) and the cells from the peritoneal cavity are recovered by lavage with 20 ml of buffer (Eagles MEM containing 30 mM HEPES adjusted to pH 7.4 with NaOH). The cells are pelleted (350 x g, 5 min.), resuspended in buffer with vigorous shaking, filtered, through lens paper, recentrifuged and finally suspended in buffer at a concentration of 10 cells/ml. A 500  $\mu$ l aliquot of PMN suspension and test compound are preincubated for 2 minutes at 37°C, followed by the addition of 10  $\mu$ M A-23187. The suspension is stirred for an additional 4 minutes then bioassayed for  $LTB_4$  content by adding an aliquot to a second 500  $\mu$ l portion of the PMN at 37°C. The  $LTB_4$  produced in the first incubation

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causes aggregation of the second PMN, which is measured as a change in light transmission. The size of the assay aliquot is chosen to give a submaximal transmission change (usually -70%) for the untreated control. The percentage inhibition of  $LTB_4$  formation is calculated from the ratio of transmission change in the sample to the transmission change in the compound-free control.

The cytoprotective activity of a compound may be observed in both animals and man by noting the increased resistance of the gastrointestinal mucosa to the noxious effects of strong irritants, for example, the ulcerogenic effects of aspirin or indomethacin. In addition to lessening the effect of non-steroidal anti-inflammatory drugs on the gastrointestinal tract, animal studies show that cytoprotective compounds will prevent gastric lesions induced by oral administration of strong acids, strong bases, ethanol, hypertonic saline solutions and the like.

Two assays can be used to measure cytoprotective ability. These assays are; (A) an ethanol-induced lesion assay and (B) an indomethacin-induced ulcer assay.

#### A. Ethanol-Induced Gastric Ulcer Assay

Twenty-four hour fasted Sprague-Dawley (S.D.) rats are perorally (p.o.) dosed with 1.0 ml absolute ethanol. Fifteen to thirty minutes prior to ethanol administration, groups of rats each receive either an aqueous vehicle (aqueous methylcellulose 5% wt.) or

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the test compound at various doses perorally. One hour later, the animals are sacrificed and stomach mucosae are examined for resulting lesions.

5. B. Indomethacin-Induced Ulcer Assay

Indomethacin, 10 mg/kg p.o., is used to induce ulcers in 24 hour fasted S.D. rats. Fifteen minutes prior to indomethacin administration, groups of rats each receive either an aqueous vehicle (5% by weight methylcellulose) or the test compound at various doses perorally. Four hours later the animals are sacrificed and stomach mucosae are examined for resulting ulcers.

The magnitude of a prophylactic or therapeutic dose of a compound of Formula I or Ia will, of course, vary with the nature of the severity of the condition to be treated and with the particular compound of Formula I or Ia and its route of administration. In general, the daily dose range for anti-asthmatic, anti-allergic, anti-inflammatory, or anti-thrombotic use lies within the range of from about 0.01 mg to about 100 mg per kg body weight of a mammal.

The exact amount of a compound of Formula I or Ia to be used as a cytoprotective agent will depend on, inter alia, whether it is being administered to heal damaged cells or to avoid future damage, on the nature of the damaged cells (e.g., gastro-intestinal ulcerations vs. nephrotic necrosis), and on the nature of the causative agent. An example of use of a compound of Formula I or Ia to avoid

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future damage is co-administration with a non-steroidal anti-inflammatory drug (for example, indomethacin).

5       The effective daily dosage level for compounds of Formulae I or Ia inducing cytoprotection in mammals, especially humans, will generally range from about 0.002 mg/kg to about 100 mg/kg, preferably from about 0.02 mg/kg to about 30 mg/kg. The dosage may be administered in single or divided individual  
10       doses.

Any suitable route of administration may be employed for providing a mammal, especially a human with an effective dosage of a compound of Formula I or Ia. For example, oral, rectal, transdermal,  
15       parenteral, intramuscular, intravenous and the like may be employed. Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules and the like.

The pharmaceutical compositions of the  
20       present invention comprise a compound of Formula I or Ia as an active ingredient or a pharmaceutically acceptable salt thereof, and may also contain a pharmaceutically acceptable carrier and optionally other therapeutic ingredients. The term "pharma-  
25       ceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from inorganic bases include sodium, potassium, lithium, ammonium, calcium, magnesium,  
30       ferrous, zinc, copper, manganous, aluminum, ferric, manganic salts and the like. Particularly preferred are the ammonium, potassium, sodium, calcium and

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magnesium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, tromethamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylene-diamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, N-ethylpiperidine, polyamine resins and the like. The compositions include compositions suitable for oral, rectal, ophthalmic, pulmonary, nasal, dermal, topical or parenteral (including subcutaneous, intramuscular and intravenous) administration, although the most suitable route in any given case will depend on the nature and severity of the conditions being treated and on the nature of the active ingredient. They may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy.

For use where a composition for intravenous administration is employed, a suitable dosage range for anti-asthmatic, anti-inflammatory or anti-allergic use is from about 0.01 mg to about 20 mg (preferably from about 0.1 mg to about 10 mg) of a compound of Formula I or Ia per kg of body weight per day and for cytoprotective use from about 0.002 mg to about 100 mg (preferably from about 0.02 mg to about 30 mg and more preferably from about 0.1 mg to about

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10 mg) of a compound of Formula I or Ia per kg of  
body weight per day. In the case where an oral  
composition is employed, a suitable dosage range for  
anti-asthmatic, anti-inflammatory or anti-allergic  
5 use is, e.g. from about 1 to about 100 mg of a  
compound of Formula I or Ia per kg of body weight per  
day, preferably from about 5 mg to about 40 mg per kg  
and for cytoprotective use from about 0.01 mg to  
about 100 mg (preferably from about 0.1 mg to about  
10 30mg and were preferably from about 0.1 mg to about  
10 mg) of a compound of Formula I or Ia per kg of  
body weight per day.

For administration by inhalation, the  
compounds of the present invention are conveniently  
15 delivered in the form of an aerosol spray presenta-  
tion from pressurized packs or a nebuliser. The  
preferred composition for inhalation is a powder  
which may be formulated as a cartridge from which the  
powder composition may be inhaled with the aid of a  
20 suitable device. In the case of a pressurized  
aerosol, the dosage unit may be determined by  
providing a valve to deliver a metered amount.

In practical use, a compound of Formula I or  
Ia can be combined as the active ingredient in  
25 intimate admixture with a pharmaceutical carrier  
according to conventional pharmaceutical compounding  
techniques. The carrier may take a wide variety of  
forms depending on the form of preparation desired  
for administration, e.g., oral or intravenous. In  
30 preparing the compositions for oral dosage form, any  
of the usual pharmaceutical media may be employed,  
such as, for example, water glycols, oils, alcohols,



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flavoring agents, preservatives, coloring agents and the like in the case of oral liquid preparations, such as, for example, suspensions, elixirs and solutions; or carriers such as starches, sugars, 5 diluents, granulating agents, lubricants, binders, disintegrating agents and the like in the case of oral solid preparations such as, for example, powders, capsules and tablets. Because of their ease of administration, tablets and capsules represent the 10 most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be sugar coated or enteric coated by standard techniques.

In addition to the common dosage forms set 15 out above, the compounds of Formula I or Ia may also be administered by controlled release means and/or delivery devices such as those described in U.S. Patent Nos. 3,845,770; 3,916,899; 3,536,809; 3,598,123; 3,630,200 and 4,008,719, the disclosure of 20 which is hereby incorporated herein by reference.

Pharmaceutical compositions of the present invention suitable for oral administration and by inhalation in the case of asthma therapy may be presented as discrete units such as capsules, cachets 25 or tablets each containing a predetermined amount of the active ingredient, as a powder or granules or as a solution or a suspension in an aqueous liquid, a non-aqueous liquid, an oil-in-water emulsion or a water-in-oil liquid emulsion. Such compositions may 30 be prepared by any of the methods of pharmacy but all methods include the step of bringing into association

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the active ingredient with the carrier which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid  
5 carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation. For example, a tablet may be prepared by compression or molding, optionally with one or more accessory ingredients. Compressed tablets  
10 may be prepared by compressing in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, lubricating, surface active or dispersing agent. Molded tablets may be made by  
15 molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Desirably, each tablet contains from about 25 mg to about 500 mg of the active ingredient and each cachet or capsule contains from about 25 to  
20 about 500 mg of the active ingredient.

The following are examples of representative pharmaceutical dosage forms for the compounds of Formula I or Ia:

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	<u>Injectable Suspension</u>	<u>mg/ml</u>
	Compound of Formula I or Ia	2.0
	Methylcellulose	5.0
	Tween 80	0.5
5	Benzyl alcohol	9.0
	Methyl paraben	1.8
	Propyl paraben	0.2
	Water for injection to a total volume of 1 ml	
10	<u>Tablet</u>	<u>mg/tablet</u>
	Compound of Formula I or Ia	25.0
	Microcrystalline Cellulose	325.0
	Providone	14.0
	Microcrystalline Cellulose	90.0
15	Pregelatinized Starch	43.5
	Magnesium Stearate	<u>2-2.5</u>
		500
	<u>Capsule</u>	<u>mg/capsule</u>
20	Compound of Formula I or Ia	25.0
	Lactose Powder	573.5
	Magnesium Stearate	<u>1-1.5</u>
		600

- 25                    In addition to the compounds of Formula I or Ia, the pharmaceutical compositions of the present invention can also contain other active ingredients, such as non-steroidal anti-inflammatory drugs (NSAIDs), peripheral analgesic agents such as
- 30    zomepirac, diflunisal and the like, cyclooxygenase inhibitors, leukotriene antagonists, leukotriene biosynthesis inhibitors, H<sub>2</sub>-receptor antagonists,

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antihistaminic agents, prostaglandin antagonists, ACE inhibitors, and thromboxane synthetase inhibitors. The weight ratio of the compound of the Formula I or Ia to the second active ingredient may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used. Thus, for example, when a compound of the Formula I or Ia is combined with a second active ingredient the weight ratio of the compound of the Formula I or Ia to the second ingredient will generally range from about 1000:1 to about 1:1000, preferably from 200:1 to 1:200. Combinations of a compound of the Formula I or Ia and other active ingredients will generally be within the aforementioned range, but in each case, an effective dose of each active ingredient should be used.

NSAIDs can be characterized into five groups:

- (1) the propionic acid derivatives;
- (2) the acetic acid derivatives;
- (3) the fenamic acid derivatives;
- (4) the biphenylcarboxylic acid derivatives;

and

- (5) the oxicams

or a pharmaceutically acceptable salt thereof.

The propionic acid derivatives which may be used comprise: ibuprofen, ibuprofen aluminum, indoprofen, ketoprofen, naproxen, benoxaprofen, flurbiprofen, fenoprofen, fenbufen, ketoprofen, indoprofen, piroprofen, carprofen, oxaprozin, pranoprofen, miroprofen, tiroxaprofen, suprofen, alminoprofen, tiaprofenic acid, fluprofen and bucloxic

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acid. Structurally related propionic acid derivatives having similar analgesic and anti-inflammatory properties are also intended to be included in this group.

5           Thus, "propionic acid derivatives" as defined herein are non-narcotic analgesics/non-steroidal anti-inflammatory drugs having a free  $-\text{CH}(\text{CH}_3)\text{COOH}$  or  $-\text{CH}_2\text{CH}_2\text{COOH}$  group (which optionally can be in the form of a pharmaceutically acceptable salt group, 10 e.g.,  $-\text{CH}(\text{CH}_3)\text{COO}^-\text{Na}^+$  or  $-\text{CH}_2\text{CH}_2\text{COO}^-\text{Na}^+$ ), typically attached directly or via a carbonyl function to a ring system, preferably to an aromatic ring system.

          The acetic acid derivatives which may be 15 used comprise: indomethacin, which is a preferred NSAID, sulindac, tolmetin, zomepirac, diclofenac, fenclofenac, alclofenac, ibufenac, isoxepac, furofenac, tiopinac, zidometacin, acemetacin, fentiazac, clidanac, oxpinac, and fenclozic acid. 20 Structurally related acetic acid derivatives having similar analgesic and antiinflammatory properties are also intended to be encompassed by this group.

          Thus, "acetic acid derivatives" as defined herein are non-narcotic analgesics/non-steroidal anti- 25 inflammatory drugs having a free  $-\text{CH}_2\text{COOH}$  group (which optionally can be in the form of a pharmaceutically acceptable salt group, e.g.  $-\text{CH}_2\text{COO}^-\text{Na}^+$ ), typically attached directly to a ring system, preferably to an aromatic or heteroaromatic ring system.

30           The fenamic acid derivatives which may be used comprise: mefenamic acid, meclofenamic acid, flufenamic acid, niflumic acid and tolfenamic acid.

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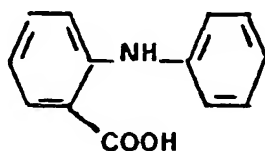
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Structurally related fenamic acid derivatives having similar analgesic and anti-inflammatory properties are also intended to be encompassed by this group.

Thus, "fenamic acid derivatives" as defined  
5 herein are non-narcotic analgesics/non-steroidal anti-inflammatory drugs which contain the basic structure:

10

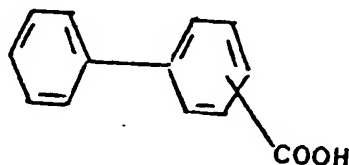


which can bear a variety of substituents and in which the free -COOH group can be in the form of a  
15 pharmaceutically acceptable salt group, e.g., -COO<sup>-</sup>Na<sup>+</sup>.

The biphenylcarboxylic acid derivatives which can be used comprise: diflunisal and flufenisal. Structurally related biphenylcarboxylic  
20 acid derivatives having similar analgesic and anti-inflammatory properties are also intended to be encompassed by this group.

Thus, "biphenylcarboxylic acid derivatives" as defined herein are non-narcotic analgesics/non-steroidal anti-inflammatory drugs which contain the  
25 basic structure:

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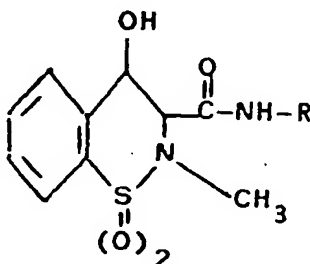
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which can bear a variety of substituents and in which the free -COOH group can be in the form of a pharmaceutically acceptable salt group, e.g., -COO<sup>-</sup>Na<sup>+</sup>.

5           The oxicams which can be used in the present invention comprise: piroxicam, sudoxicam, isoxicam and 4-hydroxyl-1,2-benzothiazine 1,1-dioxide 4-(N-phenyl)-carboxamide. Structurally related oxicams having similar analgesic and anti-inflammatory  
10 properties are also intended to be encompassed by this group.

Thus, "oxicams" as defined herein are non-narcotic analgesics/non-steroidal anti-inflammatory drugs which have the general formula:

15



20

wherein R is an aryl or heteroaryl ring system.

The following NSAIDs may also be used:

25   acemetacin, alminoprofen, amfenac sodium, aminoprofen, anitrazafen, antrafenine, auranofin, bendazac lysinate, benzydamine, beprozin, broperamole, bufezolac, carprofen, cinmetacin, ciproquazone, clidanac, cloximate, dazidamine, deboxamet,  
30   delmetacin, detomidine, dexindoprofen, diacerein, di-fisalamine, difenpyramide, emorfazone, enfenamic acid, enolicam, epirizole, etersalate, etodolac,

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etofenamate, fanetizole mesylate, fenclofenac,  
fenclorac, fendosal, fenflumizole, fentiazac,  
feprazone, floctafenine, flunixin, flunoxaprofen,  
fluproquazone, fopirtoline, fosfosal, furclopufen,  
5 furofenac, glucametacin, guaimesal, ibuproxam,  
isofezolac, isonixim, isoprofen, isoxepac, isoxicam,  
lefetamine HCl, leflunomide, lofemizole, lonazolac  
calcium, lotifazole, loxoprofen, lysin clonixinate,  
meclofenamate sodium, meseclazone, miroprofen,  
10 nabumetone, nictindole, nimesulide, orpanoxin,  
oxametacin, oxapadol, oxaprozin, perisoxal citrate,  
pimeprofen, pimetacin, piproxen, pirazolac,  
pirfenidone, pirprofen, pranoprofen, proglumetacin  
maleate, proquazone, pyridoxiprofen, sudoxicam,  
15 suprofen, talmetacin, talniflumate, tenoxicam,  
thiazolinobutazone, thielavin B, tiaprofenic acid,  
tiaramide HCl, tiflamizole, timegadine, tioxaprofen,  
tolfenamic acid, tolpadol, tryptamid, ufenamate, and  
zidometacin.

20 The following NSAIDs, designated by company  
code number, may also be used:

480156S, AA861, AD1491, AD1590, AFP802, AFP860,  
AHR6293, AI77B, AP504, AU8001, BAYo8276, BPPC,  
BW540C, BW755C, CHINOIN 127, CN100, CO893XX, CPP,  
25 D10242, DKA9, DV17, EB382, EGYT2829, EL508, F1044,  
FZ, GP53633, GP650, GV3658, HG/3, ITC1, ITF, ITF182,  
KB1043, KC8973, KCNTEI6090, KME4, LA2851, LT696,  
LU20884, M7074, MED15, MG18311, MR714, MR897, MY309,  
NO164, ONO3144, PR823, PV102, PV108, QZ16, R830,  
30 RS2131, RU16029, RU26559, RUB265, SCR152, SH440,  
SIR133, SIR136, SIR92, SPAS510, SQ27239, ST281,  
SX1032, SY6001, SaH46798, TA60, TAI901, TEI615,



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TVX2706, TVX960, TZI615, U60257, UR2310, WY23205,  
WY41770, YM09561, YM13162, YS1033, and ZK31945.

Finally, NSAIDs which may also be used  
include the salicylates, specifically aspirin, and  
5 the phenylbutazones, and pharmaceutically acceptable  
salts thereof.

Pharmaceutical compositions comprising the  
Formula I or Ia compounds may also contain other  
inhibitors of the biosynthesis of the leukotrienes  
10 such as are disclosed in EP 138,481 (April 24, 1985),  
EP 115,394 (August 8, 1984), EP 136,893 (April 10,  
1985), and EP 140,709 (May 8, 1985), which are hereby  
incorporated herein by reference.

The compounds of the Formula I or Ia may  
15 also be used in combination with leukotriene  
antagonists such as those disclosed in EP 106,565  
(April 25, 1984) and EP 104,885 (April 4, 1984),  
which are hereby incorporated herein by reference and  
others known in the art such as those disclosed in  
20 European Patent Application Nos. 56,172 and 61,800;  
and in U.K. Patent Specification No. 2,058,785, which  
are hereby incorporated herein by reference.

Pharmaceutical compositions comprising the  
Formula I or Ia compounds may also contain as the  
25 second active ingredient, antihistaminic agents such  
as benadryl, dramamine, histadyl, phenergan and the  
like. Alternatively, they may include other  
prostaglandin antagonists such as those disclosed in  
European Patent Application 11,067 (May 28, 1980) or  
30 other thromboxane antagonists such as those disclosed  
in U.S. 4,237,160. They may also contain histidine

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decarboxyase inhibitors such as  $\alpha$ -fluoromethyl-histidine, described in U.S. 4,325,961. The compounds of the Formula I may also be advantageously combined with an  $H_1$  or  $H_2$ -receptor antagonist, such as for instance cimetidine, ranitidine, 5 terfenadine, famotidine, aminothiadiazoles disclosed in EP 40,696 (December 2, 1981) and like compounds, such as those disclosed in U.S. Patent Nos. 4,283,408; 4,362,736; 4,394,508; and a pending 10 application, U.S.S.N. 301,616, filed September 14, 1981. The pharmaceutical compositions may also contain a  $K^+/H^+$  ATPase inhibitor such as omeprazole, disclosed in U.S. Pat. 4,255,431, and the like. Each of the references referred to in this 15 paragraph is hereby incorporated herein by reference.

When the second active ingredient in compositions of this invention is a thromboxane synthetase inhibitor, such inhibitor can be as described in UK 2,038,821 (e.g., UK 37248 and 20 dazoxiben hydrochloride), U.S.P. 4,217,357 (e.g., UK 34787), U.S.P. 4,444,775 (e.g., CGS 13080), U.S.P. 4,226,878 (e.g., ONO 046), U.S.P. 4,495,357 (e.g., U63557A) U.S.P. 4,273,782 (e.g., UK-38485), or EP 98,690 (e.g., CV-4151).

25 An embodiment of the invention is a cardiovascular composition useful for treating arterial thrombosis which comprises an antithrombotic compound of the Formula I or Ia.

A further embodiment of the invention is a 30 cardiovascular composition useful for treating

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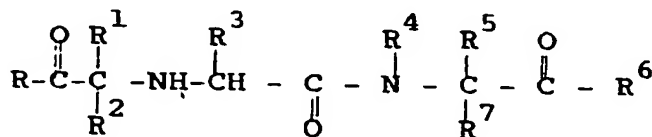
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arterial thrombosis which comprises: (1) the antithrombotic Formula I or Ia compound defined above; and, (ii) an angiotensin converting enzyme (ACE) inhibitor compound which is a member of the group: carboxyalkyl dipeptide derivatives; captopril [1-(3-mercapto-2-methyl-1-oxopropyl)-L-proline]; 2-[N-(S)-1-ethoxycarbonyl-3-phenylpropyl)-S-alanyl]-cis,endo-2-azabicyclo[3.3.0]octane-3(S)-carboxylic acid; N-((S)-1-ethoxycarbonyl-3-phenylpropyl)-L-alanyl-N-(2-indanyl)-glycine; 1-(N-[(S)-1-ethoxycarbonyl-3-phenylpropyl]-L-alanyl)-cis, syn-octahydro-(H-indole-2-S)-carboxylic acid; 2-(N-[(S)-1-ethoxycarbonyl-3-phenylpropyl]-L-alanyl)-1,2,3,4-tetrahydro-iso-isoquinoline-3(S)-carboxylic acid; and, 1-carboxymethyl-3(S)-(1(S)-ethoxycarbonyl-3-phenylpropylamino)-2,3,4,5-tetrahydro-1H[1]-benzazepine-2-one.

In particular the class of ACE inhibitors which have been found to have a potentiating effect when used in combination with the Formula I or Ia compounds are those disclosed in U.S. Patent 4,374,829, which also discloses methods for their preparation and which patent is incorporated herein by reference and which compounds are generally represented by the Formula XI:



30

XI

wherein

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- R and R<sup>6</sup> are the same or different and are hydroxy,  
 lower C<sub>1</sub>-C<sub>8</sub> alkoxy;  
 lower C<sub>1</sub>-C<sub>8</sub> alkenoxy;  
 dilower C<sub>1</sub>-C<sub>8</sub> alkylamino lower C<sub>1</sub>-C<sub>8</sub>  
 5 alkoxy (dimethylaminoethoxy);  
 acylamino lower C<sub>1</sub>-C<sub>8</sub> alkoxy (acetyl-  
 aminoethoxy);  
 acyloxy lower C<sub>1</sub>-C<sub>8</sub> alkoxy (pivaloyloxy-  
 methoxy);  
 10 aryloxy, wherein the aryl is C<sub>6</sub> or C<sub>10</sub>  
 such as phenoxy;  
 arlower C<sub>1</sub>-C<sub>8</sub> alkoxy, such as benzyloxy;  
 substituted aryloxy or substituted  
 arlower-C<sub>1</sub>-C<sub>8</sub> alkoxy wherein the aryl is  
 15 C<sub>6</sub> or C<sub>10</sub> and the substituent is methyl,  
 halo or methoxy;  
 amino;  
 lower C<sub>1</sub>-C<sub>8</sub> alkylamino;  
 dilower C<sub>1</sub>-C<sub>8</sub> alkylamino;  
 20 hydroxyamino;  
 arlower C<sub>1</sub>-C<sub>8</sub> alkylamino wherein the  
 aryl group is C<sub>6</sub>-C<sub>10</sub> such as benzylamino;  
 R<sup>1</sup> is hydrogen;  
 hydrocarbon of from 1 to 20 carbon atoms  
 25 which include branched and unsaturated  
 (such as allyl) groups;  
 C<sub>3</sub>-C<sub>10</sub> cycloalkyl;  
 substituted lower C<sub>1</sub>-C<sub>8</sub> alkyl wherein  
 the substituent can be halo, hydroxy,  
 30 lower C<sub>1</sub>-C<sub>8</sub> alkoxy, aryloxy wherein  
 the aryl is C<sub>6</sub>-C<sub>10</sub> such as phenoxy.

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- amino, dilower  $C_1-C_8$  alkylamino, acylamino such as acetamido and benzamido, arylamino wherein the aryl is  $C_6$  or  $C_{10}$ , guanidino,
- 5 imidazolyl, indolyl, mercapto, lower  $C_{1-8}$  alkylthio, arylthio wherein the aryl is  $C_6$  or  $C_{10}$  such as phenylthio, carboxy or carboxamido, carbolower  $C_{1-8}$  alkoxy;
- 10 aryl of  $C_6-C_{10}$  such as phenyl or naphthyl;
- substituted aryl of  $C_6-C_{10}$  such as phenyl wherein the substituent is lower  $C_1-C_8$  alkyl, lower  $C_1-C_8$  alkoxy
- 15 or halo,
- unsubstituted or substituted arloweralkyl, arloweralkenyl, heteroarlower alkyl, or heteroarlower alkenyl, wherein aryl groups are  $C_6$  or  $C_{10}$ , the alkyl groups are  $C_2-C_8$ , and the heteroatoms are one of O, N or S and the the substituent(s) is halo, dihalo, lower  $C_1-C_8$  alkyl, hydroxy, lower  $C_1-C_8$  alkoxy, amino, aminomethyl,
- 20 acylamino (acetylamino or benzoylamino) dilower  $C_1-C_8$  alkylamino, lower  $C_1-C_8$  alkylamino, carboxyl, halolower  $C_1-C_8$  alkyl, cyano or sulfonamido;
- 25
- 30 arlower  $C_1-C_8$  alkyl or heteroarlower  $C_1-C_8$  alkyl wherein the aryl group is  $C_6$  or  $C_{10}$  and the heteroatom is

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one of O, N or S, substituted on the  
alkyl portion by amino or acylamino  
(acetyl amino or benzoyl amino);

- 5         $R^2$  and  $R^7$  are the same or different and are  
hydrogen or lower  $C_1-C_8$  alkyl;
- 10        $R^3$  is hydrogen, lower  $C_1-C_8$  alkyl, phenyl  
lower  $C_1-C_8$  alkyl, aminomethyl phenyl  
lower  $C_1-C_8$  alkyl, hydroxy phenyl lower  
 $C_1-C_8$  alkyl, hydroxy lower  $C_1-C_8$   
15       alkyl, acylamino lower  $C_1-C_8$  alkyl (such  
as benzoyl amino lower  $C_1-C_8$  alkyl,  
acetyl amino lower  $C_1-C_8$  alkyl), amino  
lower  $C_1-C_8$  alkyl, dimethyl amino lower  
 $C_1-C_8$  alkyl, halo lower  $C_1-C_8$  alkyl,  
20       guanidino lower  $C_1-C_8$  alkyl, imidazolyl  
lower  $C_1-C_8$  alkyl, indolyl lower  
 $C_1-C_8$  alkyl, mercapto lower  $C_1-C_8$   
alkyl, lower  $C_1-C_8$  alkyl thio lower  
 $C_1-C_8$  alkyl;
- 25        $R^4$  is hydrogen or lower  $C_1-C_8$  alkyl;  
 $R^5$  is hydrogen, lower  $C_1-C_8$  alkyl, phenyl,  
phenyl lower  $C_1-C_8$  alkyl, hydroxy phenyl  
lower  $C_1-C_8$  alkyl, hydroxy lower  
 $C_1-C_8$  alkyl, amino lower  $C_1-C_8$   
30       alkyl, guanidino lower  $C_1-C_8$  alkyl,  
imidazolyl lower  $C_1-C_8$  alkyl, indolyl  
lower  $C_1-C_8$  alkyl, mercapto lower  
 $C_1-C_8$  alkyl or lower  $C_1-C_8$  alkyl  
thio lower  $C_1-C_8$  alkyl; or,
- 30        $R^4$  and  $R^5$  may be connected together to form an  
alkylene bridge of from 2 to 4 carbon atoms,  
an alkylene bridge of from 2 to 3 carbon

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atoms and one sulfur atom, an alkylene  
bridge of from 3 to 4 carbon atoms  
containing a double bond or an alkylene  
bridge as above substituted with hydroxy,  
5 lower C<sub>1</sub>-C<sub>8</sub> alkoxy, lower C<sub>1</sub>-C<sub>8</sub>  
alkyl or dilower C<sub>1</sub>-<sub>8</sub> alkyl;  
and, the pharmaceutically acceptable salts thereof.

Preferred ACE inhibitor compounds of Formula  
10 VI are those wherein:  
R and R<sup>6</sup> can each independently be hydroxy, lower  
alkoxy, lower alkenoxy, arloweralkyloxy,  
amino, diloweralkylamino lower alkoxy,  
acylamino lower alkoxy or acyloxy lower  
15 alkoxy;  
R<sup>1</sup> is hydrogen,  
alkyl of from 1 to 20 carbon atoms,  
including branched, cyclic and unsaturated  
alkyl groups;  
20 substituted lower alkyl wherein the  
substituent is halo, hydroxy, lower alkoxy,  
aryloxy, amino, loweralkylamino,  
diloweralkylamino, acylamino, arylamino,  
guanidino, imidazoyle, indolyle, mercapto,  
25 loweralkylthio, arylthio, carboxy,  
carboxamido or carbolower alkoxy;  
phenyl;  
substituted phenyl wherein the substituent  
is lower alkyl, lower alkoxy or halo;  
30 arloweralkyl or heteroarylloweralkyl  
arloweralkenyl or heteroarloweralkenyl,  
substituted arloweralkyl, substituted

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heteroaryl lower alkyl, substituted  
aryl lower alkenyl or substituted  
heteroaryl lower alkenyl;  
wherein the substituent is halo or dihalo  
5 lower alkyl, hydroxy, lower alkoxy, amino,  
aminomethyl, acylamino, dialkylamino,  
lower alkylamino, carboxyl, halo alkyl, cyano  
or sulfonamido;  
aryl lower alkyl or heteroaryl lower alkyl  
10 substituted on the alkyl portion by amino or  
acylamino;  
R<sup>2</sup> and R<sup>7</sup> are hydrogen;  
R<sup>3</sup> is lower alkyl, amino lower alkyl, imidazolyl,  
lower alkyl, halo lower alkyl;  
15 R<sup>4</sup> and R<sup>5</sup> are joined to form an alkylene bridge  
of from 2 to 4 carbon atoms or an alkylene  
bridge of from 2 or 3 carbon atoms and one  
sulfur atom or an alkylene bridge of from 2  
to 3 carbon atoms and one sulfur atom or an  
20 alkylene bridge of from 3 to 4 carbon atoms  
containing a double bond or an alkylene  
bridge of from 3 to 4 carbon atoms contain-  
ing a double bond or an alkylene bridge as  
above substituted with hydroxy, lower alkoxy  
25 or lower alkyl;  
or the pharmaceutically acceptable salts thereof  
wherein said aryl is a member selected from the group  
consisting of phenyl or naphthyl and said heteroaryl  
is a member selected from the group consisting of  
30 pyridyl, thienyl, furyl, indolyl, benzthienyl,  
imidazolyl, or thiazolyl.



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More preferred are those antihypertensive compounds of Formula VI wherein:

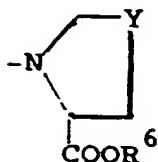
R and R<sup>6</sup> can each independently be hydroxy, lower alkoxy, lower alkenoxy, arloweralkyloxy, amino, diloweralkylamino lower alkoxy, acylamino lower alkoxy or acyloxy lower alkoxy;

R<sup>1</sup> is alkyl having from 1-8 carbon atoms, substituted lower alkyl wherein the alkyl group has 1-5 carbon atoms and the substituent is amino, arylthio, aryloxy or arylamino, aralkyl or heteroaralkyl wherein the alkyl portion has 1-3 carbon atoms, substituted aralkyl or heteroaralkyl wherein the alkyl groups have 1-3 carbon atoms and the substituent(s) is halo, dihalo, amino, aminoalkyl, hydroxy, lower alkoxy or lower alkyl;

R<sup>2</sup> and R<sup>7</sup> are hydrogen;

R<sup>3</sup> is lower alkyl or amino lower alkyl;

R<sup>4</sup> and R<sup>5</sup> can be joined together through the carbon and nitrogen atoms to which they are attached to form a ring of the formula:



wherein Y is CH<sub>2</sub>, S, or CH-OCH<sub>3</sub> or the pharmaceutically acceptable salts thereof wherein said aryl is a member selected from

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the group consisting of phenyl or naphthyl  
and said heteroaryl is a member selected  
from the group consisting of pyridyl,  
thienyl, furyl, indolyl, benzthienyl,  
5 imidazolyl or thiazolyl.

Still more preferred antihypertensive  
compounds of Formula VI are those wherein:  
R and R<sup>6</sup> can each independently be hydroxy, lower  
10 alkoxy, aralkyloxy;  
R<sup>2</sup> and R<sup>7</sup> are hydrogen;  
R<sup>3</sup> is methyl, aminoloweralkyl;  
R<sup>4</sup> and R<sup>5</sup> are joined through the carbon and  
nitrogen atoms to form proline,  
15 4-thiaproline or 4-methoxyproline and;  
R<sup>1</sup> is alkyl having from 1-8 carbon atoms,  
substituted lower alkyl wherein the alkyl  
group has 1-5 carbon atoms and the  
substituent is amino, arylthio or aryloxy,  
20 aralkyl or heteroaralkyl wherein the alkyl  
portion has 1-3 carbon atoms, substituted  
aralkyl or heteroaralkyl wherein the alkyl  
groups have 1-3 carbon atoms and the  
substituent(s) is halo, dihalo, amino,  
25 aminoalkyl, hydroxy, lower alkoxy or lower  
alkyl;

and the pharmaceutically acceptable salts thereof  
wherein said aryl is a member selected from the group  
consisting of phenyl or naphthyl and said heteroaryl  
30 is a member selected from the group consisting of  
pyridyl, thienyl, furyl, indolyl, benzthienyl,  
imidazolyl or thiazolyl.

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Examples of Formula I or Ia compounds are set forth above on pages 38-41.

Examples of Formula VI compounds are:

- 5 (i) N-(1-carboxy-3-phenylpropyl)-L-alanyl-L-proline;
- (ii) N-(1-ethoxycarbonyl-3-phenylpropyl)-L-alanyl-L-proline;
- (iii) N-(1-ethoxycarbonyl-4-methylpentyl)-L-alanyl-L-proline;
- 10 (iv) N-(1-carboxy-5-aminopentyl)-L-alanyl-L-proline;
- (v) N- $\alpha$ -(1-carboxy-3-phenylpropyl)-L-lysyl-L-proline;
- 15 (vi) N- $\alpha$ -(1-ethoxycarbonyl-3-phenylpropyl)-L-lysyl-L-proline;
- (vii) N- $\alpha$ -[1-carboxy-3-(3-indolyl)-propyl]-L-lysyl-L-proline;
- (viii) N- $\alpha$ -[1-carboxy-3-(4-chlorophenyl)-propyl]-L-lysyl-L-proline;
- 20 (ix) N- $\alpha$ -[1-carboxy-2-phenylthioethyl]-L-lysyl-L-proline;
- (x) N- $\alpha$ -[1-carboxy-3-(4-chlorophenyl)-propyl]-L-lysyl-trans-4-methoxy-L-proline;
- (xi) N- $\alpha$ -[1-carboxy-5-aminopentyl]-L-lysyl-L-proline;
- 25 (xii) N- $\alpha$ -(1-carboxy-3-phenylpropyl)-L-ornithyl-L-proline;
- (xiii) ethyl N-(1-ethoxycarbonyl-3-phenylpropyl)-L-alanyl-L-prolinate hydrochloride;
- 30 (xiv) N-[1-(ethoxycarbonyl)-3-(4-imidazolyl)propyl]-L-alanyl-L-proline.

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- (xv) N-[1-carboxy-3-(4-imidazolyl)propyl]-L-lysyl-L-proline;
- (xvi) N-(1(S)-carboxy-3-phenylpropyl)-L-alanyl-L-proline;
- 5 (xvii) N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanyl-L-proline maleate salt;
- (xviii) N- $\alpha$ -(1(S)-carboxy-3-phenylpropyl)-L-lysyl-L-proline;
- (xix) ethyl N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanyl-L-prolinate hydrochloride;
- 10 (xx) N- $\alpha$ -(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-lysyl-L-proline.

The above-described Formula VI compounds, their use and the method of preparation thereof are disclosed in U.S. Patent 4,374,829 the disclosure of which is hereby incorporated herein by reference.

The resolution of certain Formula I and Ia compounds into their optically pure enantiomers is as disclosed in U.S. Patents 4,424,355 and 4,435,579 which have been incorporated herein by reference.

The combination composition of the invention can contain varying amounts of the Formula I or Ia (i) antithrombotic compound and Formula VI (ii) antihypertensive compounds. The weight ratio of (i):(ii) can range from about 25 to 1; preferably from about 10 to 1. In addition to the active ingredients of (i) alone or of (i) and (ii) in combination, the compositions of the invention can also contain other conventional pharmaceutically acceptable compounding ingredients, as necessary or desired. Such ingredients are generally referred to as carriers or diluents. Conventional procedures for

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preparing such compositions in appropriate dosage forms can be utilized. Whatever the dosage form, it will contain a pharmaceutically effective amount of the present composition.

5           The combination compositions can be administered orally or other than orally; e.g., parenterally, by insufflation, topically, rectally, etc.; using appropriate dosage forms; e.g., tablets, capsules, suspensions, solutions, and the like, for  
10 oral administration; suspension emulsions, and the like, for parenteral administration; solutions for intravenous administration; and ointments, transdermal patches, and the like, for topical administration. These compositions are formulated similarly to the  
15 compositions discussed on pages 46 to 51, above.

Treatment dosage for human beings for cardiovascular use can be varied as necessary. Generally, daily dosages of the composition of the invention can range from about 6000 to about 10 mg;  
20 preferably, from about 3000 to about 20 mg.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form for cardiovascular use will vary depending upon the host treated and the particular  
25 mode of administration. For example, a formulation intended for oral administration may contain from 5 mg to 5 gm of active agents compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of  
30 the total composition. Dosage unit forms will generally contain between from about 20 mg to about 500 mg of active ingredients.

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It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, 5 body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

The composition of this invention inhibits 10 platelet accumulation at the damaged endothelial surface via the Formula I or Ia compound. This inhibitory effect is potentiated by the presence of the antihypertensive compound.

Thus, the compositions of the invention are 15 useful in treating thrombosis and are also of value in the management of acute and chronic congestive heart failure.

In vivo testing of the composition of this invention in test animals (rabbits) can be used to 20 demonstrate that this composition is pharmaceutically effective in decreasing platelet-related arterial thrombic formation.

To demonstrate the potentiation of the antihypertensive compound on the anti-thrombotic 25 Formula I or Ia compound comprising the combination composition of the invention, the effect of these compounds on test animals (rabbits) can be determined separately and then in combination. The effect of a different class of antihypertensive agents singly and 30 in combination with the Formula I or Ia compound of the invention can also be determined for comparative purposes. The methods employed are described in a

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copending application, attorney docket no 17062, U.S. Serial No. 617,293, filed June 4, 1984, which is hereby incorporated herein by reference.

5           The following examples illustrate the preparation of the compounds of the present invention without, however, limiting the same thereto.

          All temperatures are in degrees Celsius.

10

EXAMPLE 1

A. Preparation of Hydrazine Starting Materials  
1-[(4-Chlorophenyl)methyl]-1-(4-methylphenyl)  
hydrazine

          A mixture of 10 g of p-tolylhydrazine  
15 hydrochloride, 75 ml of toluene and 11.5 ml of triethylamine was heated at reflux for 60 minutes. Then, 7.1 g of p-chlorobenzyl chloride was added. After stirring 16 hours at reflux, triethylamine hydrochloride was filtered off and washed with ethyl  
20 ether. The filtrate and washing were concentrated in vacuo and chromatographed on a silica gel column (hexane-ethylacetate, 9:1) to give 6.64 g of the title compound, (Compound No. 5 in Table 3).

25 B. Other hydrazines, similarly prepared, are also shown in Table 3.

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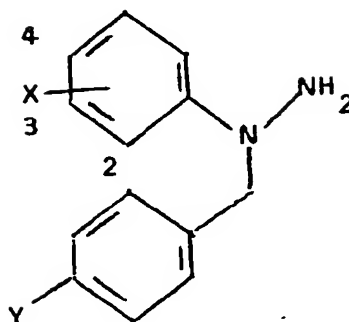
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TABLE 3Hydrazines

5

10



Compound

15

No.	X	Y	Compound Name
1.	4-F	Cl	1-[(4-chlorophenyl)-methyl]-1-(4-fluorophenyl)hydrazine hydrochloride
2.	3,5-Cl <sub>2</sub>	Cl	1-[(4-chlorophenyl)-methyl]-1-(3,5-dichlorophenyl)hydrazine hydrochloride
3.	3-OMe	Cl	1-[(4-chlorophenyl)-methyl]-1-(3-methoxyphenyl)hydrazine hydrochloride
4.	3-Me	Cl	1-[(4-chlorophenyl)-methyl]-1-(3-methylphenyl)hydrazine hydrochloride

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5	5.	4-Me	Cl	1-[(4-chlorophenyl)-methyl]-1-(4-methylphenyl)hydrazine hydrochloride
10	6.	4-Cl	Cl	1-[(4-chlorophenyl)-methyl]-1-(4-chlorophenyl) hydrazine hydrochloride
15	7.	H	Cl	1-[(4-chlorophenyl)-methyl]-1-(phenyl)hydrazine hydrochloride
20	8.	4-Br	Cl	1-[(4-chlorophenyl)-methyl]-1-(4-bromophenyl)hydrazine hydrochloride
25	9.	4-OMe	SMe	1-[(4-methylthiophenyl)-methyl]-1-(4-methoxyphenyl) hydrazine hydrochloride
30	10.	4-OMe	Cl	1-[(4-chlorophenyl)-methyl]-1-(4-methoxyphenyl) hydrazine hydrochloride
	11.	4-OMe	NO <sub>2</sub>	1-[(4-nitrophenyl)-methyl]-1-(4-methoxyphenyl)hydrazine hydrochloride

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12.                    4-F                    SMe                    1-[(4-methylthiophenyl)-  
methyl]-1-(4-fluoro-  
phenyl) hydrazine hydro-  
chloride

5

# EXAMPLE 2

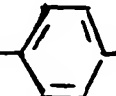
3 (or Beta)-[1-(p-Chlorobenzyl)-5-chloro-3-methyl-2-  
indolyl]-propionic acid

10 Step 1:

To 1.84 g of 1,1-[(4-chlorophenyl)methyl]-1-(4-chlorophenyl) hydrazide hydrochloride in 60 cc of tert-butanol was added 868 mg of methyl 4-oxo-hexanoate. The reaction mixture was refluxed under  
15 nitrogen for 16 hours. The resulting reaction mixture was then evaporated to dryness and the resulting residue suspended in CH<sub>2</sub>Cl<sub>2</sub>. The solid material was then filtered. The filtrate was washed  
20 with water, dried and evaporated. The resulting syrup was then chromatographed on silica gel to give 1.47 g of indole derivative (65%).

NMR: <sup>1</sup>H NMR (CDCl<sub>3</sub>): 2.25 ppm (Me, 3H, singlet); 2.43 (CH<sub>2</sub>, 2H, triplet); 3.01 (CH<sub>2</sub>, 2H, triplet); 3.64

25

(OMe, 3H, singlet); 5.29 (CH<sub>2</sub>-Cl, 2H, singlet); 6.83

(H-2' and H-6', 2H, d); 7.1 (H-6, and H-7, 2H, multiplet); 7.25 (H-3' and H-5', 2H); 7.49 (H-4, 1H, singlet).

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Step 2:

To 1.06 g of methyl ester in 350 ml of EtOH was added 169 mg of sodium hydroxide dissolved in 3 ml of H<sub>2</sub>O. The resulting solution was stirred at room temperature for 16 hours. The reaction mixture was then acidified with HCl (1N) and concentrated. The resulting solution was then extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 times). The combined organic layer was washed with brine, dried over MgSO<sub>4</sub>, and evaporated to give 1 g of solid material (100% yield). An analytical sample of this material was prepared by triturating the resulting solid material with hexane followed by a filtration (800 mg).

Analysis calculated for C<sub>19</sub>H<sub>17</sub>Cl<sub>2</sub>NO<sub>2</sub>:

C, 62.99; H, 4.74; N, 19.58

Found: C, 63.19; H, 4.78; N, 19.35.

EXAMPLE 3

3 (or Beta)-[1-(p-Chlorobenzyl)-3-methyl-5-fluoro-2-indolyl]-propionic acid

Following the procedure of Example 2, but using 1-[(4-chlorophenyl)methyl]-1-(4-fluorophenyl)-hydrazine hydrochloride and methyl 4-oxohexanoate as the starting materials and ethanol as the solvent, the title compound was prepared.

Analysis calculated for C<sub>19</sub>H<sub>17</sub>ClFNO<sub>2</sub>:

C, 65.98; H, 4.95; Cl, 10.25

Found: C, 65.56; H, 5.17; Cl, 10.52.

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EXAMPLE 4

3 (or Beta)-[1-p-Chlorobenzyl-3-methyl-4,6-dichloro-  
2-indolyl]propionic acid

5       Following the procedure of Example 2, but  
using 1-[(4-chlorophenyl)methyl]-1-(3,5-dichloro-  
phenyl)hydrazine hydrochloride and methyl  
4-oxohexanoate as the starting materials and ethanol  
as the solvent, the title compound was prepared.

Analysis calculated for  $C_{19}H_{16}O_2Cl_3N$ :

10               C, 57.52; H, 4.06

Found:    C, 57.40; H, 4.20.

EXAMPLE 5

15   3 (or Beta)-[1-(p-Chlorobenzyl)-3-methyl-4-methoxy-2-  
indolyl]propionic acid

      Following the procedure of Example 2, but  
using 1-[(4-chlorophenyl)methyl]-1-(3-methoxyphenyl)-  
hydrazine hydrochloride and ethyl 4-oxohexanoate as  
the starting materials and ethanol as the solvent,  
20   the title compound was prepared.

Analysis calculated for  $C_{20}H_{20}O_3NCl$ :

      C, 67.12; H, 5.63

Found:    C, 67.40; H, 5.43.

EXAMPLE 6

25   3 (or Beta)-[1-(p-chlorobenzyl)-3-methyl-6-methoxy-2-  
indolyl]propionic acid

      Following the procedure of Example 2, but  
using 1-[(4-chlorophenyl)methyl]-1-(5-methoxyphenyl)-  
30   hydrazine hydrochloride and methyl 4-oxohexanoate as  
the starting materials and tert-butanol as the  
solvent, the title compound was prepared.

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Analysis calculated for  $C_{20}H_{20}O_3NCl$ :

C, 67.12; H, 5.63; N, 3.91; Cl, 9.90

Found: C, 67.08; H, 5.64; N, 4.09.

5

EXAMPLE 7

3 (or Beta)-[1-(p-Chlorobenzyl)-3,4-dimethyl-2-indolyl]propionic acid and 3 (or Beta)-[1-(p-chlorobenzyl)-3,6-dimethyl-2-indolyl]propionic acid (as a mixture)

10

Following the procedure of Example 2, but using 1-[(4-chlorophenyl)methyl]-1-(3-methylphenyl)-hydrazine hydrochloride and methyl 4-oxohexanoate as the starting materials and t-butanol as the solvent, the title compounds were prepared.

15

Analysis calculated for  $C_{20}H_{20}NClO_2$ :

C, 70.26; H, 5.89; N, 4.09; Cl, 10.37

Found: C, 70.52; H, 5.57; N, 4.56; Cl, 10.03.

EXAMPLE 8

20

1-(4-Chlorobenzyl)-3-methyl-5-methoxy-2-(4'-carboxybutyl)indole

25

Following the procedure of Example 2, but using 1-[(4-chlorophenyl)methyl]-1-(4-methoxyphenyl)-hydrazine hydrochloride and methyl 6-oxooctanoate as the starting materials and methanol as the solvent, the title compound was prepared.

Analysis calculated for  $C_{22}H_{24}NO_3Cl$ :

C, 68.57; H, 6.23; N, 3.63

Found: C, 68.45; H, 6.41; N, 3.35.

30

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EXAMPLE 9

3 (or Beta)-[1-(p-Chlorobenzyl)-3,5-dimethyl-2-indolyl]propionic acid

---

5 Following the procedure of Example 2, but using 1-[(4-chlorophenyl)methyl]-1-(4-methylphenyl)-hydrazine hydrochloride and methyl 4-oxohexanoate as the reactants and ethanol as the solvent, the title compound was prepared.

Analysis calculated for  $C_{20}H_{20}O_2NCl$ :

10 C. 70.31; H. 5.90; N. 4.1; Cl. 10.37

Found: C. 70.37; H. 5.85; N. 4.10; Cl. 10.15.

EXAMPLE 10

15 1-(4-Chlorobenzyl)-3-methyl-5-methoxy-2-(3-carboxypropyl)indole

---

Following the procedure of Example 2, but using 1-[(4-chlorophenyl)methyl]-1-(4-methoxyphenyl)-hydrazine hydrochloride and methyl 5-oxoheptanoate as the starting materials and ethanol as the solvent, the title compound was prepared.

Analysis calculated for  $C_{21}H_{22}NO_3Cl$ :

C. 67.83; H. 5.92; N. 3.76

Found: C. 67.92; H. 5.97; N. 3.84.

EXAMPLE 11

25 3 (or Beta)-[1-(p-Chlorobenzyl)-3-methyl-2-indolyl]propionic acid

---

Following the procedure of Example 2, but using 1-[(4-chlorophenyl)methyl]-1-(phenyl)hydrazine hydrochloride and methyl 4-oxohexanoate as the starting materials and tert-butanol as the solvent, the title compound was prepared.

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Analysis calculated for  $C_{19}H_{18}O_2ClN$ :

C, 67.15; H, 5.33; N, 4.12; Cl, 10.43

Found: C, 67.77; H, 5.42; N, 4.48; Cl, 10.48.

5

EXAMPLE 12

3 (or Beta)-[1-(p-Chlorobenzyl)-5-bromo-3-methyl-2-indolyl]propionic acid

10

Following the procedure of Example 2, but using 1-[(4-chlorophenyl)methyl]-1-(4-bromophenyl)-hydrazine hydrochloride and methyl 4-oxohexanoate as the starting materials and t-butanol as the solvent, the title compound was prepared.

Analysis calculated for  $C_{19}H_{17}ClO_2BrN$ :

C, 56.10; H, 4.21;

15

Found: C, 56.07; H, 4.27.

EXAMPLE 13

1-(4-Thiomethylbenzyl)-5-methoxy-3-methyl-2-(2-carboxyethyl)indole

20

Following the procedure of Example 2, but using 1-[(4-methylthiophenyl)methyl]-1-(4-methoxyphenyl)hydrazine hydrochloride and methyl 4-oxohexanoate as the starting materials and tert-butanol as the solvent, the title compound was prepared.

25

Analysis calculated for  $C_{21}H_{23}NO_3S$ :

C, 68.29; H, 6.23; N, 3.79

Found: C, 68.03 H, 6.12; N, 3.76.

30

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EXAMPLE 14

1-(4-Thiomethylbenzyl)-5-methoxy-3-methyl-2-(2-carboxyethyl)indole S-oxide

5 Using the methyl ester of the title compound of Example 13 as the starting material, 250 mg were dissolved in 20 ml of dichloro methane and cooled to 0°C. Metachloroperoxybenzoic acid, 138 mg, was added and the reaction stirred at 0°C for 1 hour. 200 mg anhydrous  $\text{Ca}(\text{OH})_2$  was added and the reaction  
10 filtered and evaporated to dryness. The methyl ester so obtained was hydrolyzed according to the conditions described in Example 2.

Analysis calculated for  $\text{C}_{21}\text{H}_{23}\text{NO}_4\text{S}$ :

C, 63.45; H, 5.70; N, 3.47

15 Found: C, 63.55; H, 5.67; N, 3.32.

EXAMPLE 15

1-(4-Thiomethylbenzyl)-5-methoxy-3-methyl-2-(3-carboxypropyl)indole

20 Following the method of Example 2, but using 1-[(4-methylthiophenyl)methyl]-1-(4-methoxyphenyl)-hydrazine hydrochloride and methyl 4-oxoheptanoate as the starting materials and tert-butanol as the solvent, the title compound was prepared.

25 Analysis calculated for  $\text{C}_{22}\text{H}_{25}\text{NO}_3\text{S} \cdot 1/2 \text{H}_2\text{O}$ :

C, 67.86; H, 6.64; N, 3.50

Found: C, 66.85; H, 6.63; N, 3.31



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EXAMPLE 16

4-[1-(p-Chlorobenzyl)-3-methyl-5-fluoro-2-indolyl]-  
butanoic acid

5       Following the method of Example 2, but using  
1-[(4-chlorophenyl)methyl]-1-(4-fluorophenyl)hydrazine  
hydrochloride and methyl 5-oxoheptanoate as the  
starting materials and tert-butanol as the solvent,  
the title compound was prepared.

Analysis calculated for  $C_{20}H_{19}ClFNO_2$ :

10           C, 66.76; H, 5.32; Cl, 9.85

Found:    C, 66.89; H, 5.24; Cl, 10.26.

EXAMPLE 17

15       3 (or Beta)-[1-(p-Thiomethylbenzyl)-3-methyl-5-fluoro-  
2-indolyl]propanoic acid

20       Following the procedure of Example 2, but  
using 1-[(4-methylthiophenyl)methyl]-1-(4-fluoro-  
phenyl)hydrazine hydrochloride and methyl 4-oxo-  
hexanoate as the starting materials and tert-butanol  
as the solvent, the title compound was prepared.

Analysis calculated for  $C_{20}H_{20}O_2FSN$ :

          C, 67.20; H, 5.64; N, 3.91

Found:    C, 67.21; H, 5.91; N, 3.88.

EXAMPLE 18

25       3 (or Beta)-[1-p-Methylsulfoxylbenzyl)-3-methyl-5-  
fluoro-2-indolyl]-propanoic acid

30       Using the title compound of Example 17,  
treated according to the procedure described in  
Example 14, the title compound was obtained.

Analysis calculated for  $C_{20}H_{20}FNO_3S$ :

          C, 64.32; H, 5.39; N, 3.75

Found:    C, 64.18; H, 5.65; N, 3.48.

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EXAMPLE 19

3-[1-(4-Chlorobenzyl)-3-methyl-5-methoxy-2-indolyl]-  
butanoic acid

5       Following the method of Example 2, but using  
1-[(4-chlorophenyl)methyl]-1-(4-methoxyphenyl)-  
hydrazine hydrochloride and methyl 3-methyl-4-  
oxohexanoate as the starting materials and methanol  
as the solvent, the title compound was prepared.

Analysis calculated for  $C_{21}H_{22}NO_3Cl \cdot H_2O$ :

10           C, 64.78; H, 6.13; N, 3.59

Found:    C, 65.86; H, 6.12; N, 3.37.

EXAMPLE 20

15       3-Methyl-4-[1-p-chlorobenzyl-5-methoxy-3-methylindol-  
2-yl]butanoic acid

20       Following the method of Example 2, but using  
1-[(4-chlorophenyl)methyl]-1-(4-methoxyphenyl)hydrazine  
hydrochloride and 3-methyl-5-oxoheptanoic acid as  
the starting materials and isopropanol as the  
solvent, the title compound was prepared.

Analysis calculated for  $C_{22}H_{24}O_3NCl$ :

C, 68.48; H, 6.27; N, 3.63; Cl, 9.19

Found:    C, 68.49; H, 6.50; N, 3.55; Cl, 8.93.

25       EXAMPLE 21

3-Methyl-4-[1-p-chlorobenzyl-5-fluoro-3-methylindol-2-  
yl]butanoic acid

30       Following the method of Example 2, but using  
1-[(4-chlorophenyl)methyl]-1-(4-fluorophenyl)hydrazine  
hydrochloride and 3-methyl-4-oxoheptanoic acid as the  
starting materials and isopropanol as the solvent,  
the title compound was prepared.

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Analysis calculated for  $C_{21}H_{21}O_2NClF$ :

Calc.: C, 67.47; H, 5.66; N, 3.75; Cl, 9.48; F, 5.08

Found: C, 67.57; H, 5.90; N, 3.60; Cl, 9.44; F, 4.50

5

EXAMPLE 22

3-(1-p-Chlorobenzyl-3-methyl-5-methoxyindol-2-yl)-2,2-dimethylpropanoic acid

Following the method of Example 2, but using  
1-[(4-chlorophenyl)methyl]-1-(4-methoxyphenyl)hydrazine  
10 hydrochloride and methyl 2,2-dimethyl-4-oxohexanoate  
as the starting materials and tert-butanol as the  
solvent, the title compound was prepared.

Analysis calculated for  $C_{22}H_{24}NO_3Cl$ :

Calc.: C, 64.48; H, 6.40; N, 3.63

15 Found: C, 68.32; H, 6.37; N, 3.53.

EXAMPLE 23

3-[1-p-Chlorobenzyl-5-hydroxy-3-methylindol-2-yl]-propionic acid

20 Beginning with 3-[1-p-chlorobenzyl-5-methoxy-3-methylindol-2-yl]propionic acid which is described  
in J. Med. Chem., 1252 (1968), (2.7 g) was dissolved  
in 20 ml  $CH_2Cl_2$  at 0°C. 7.6 ml  $BBr_3$  (1M in  
 $CH_2Cl_2$ ) was added dropwise and the reaction  
25 stirred for 60 minutes. After 180 minutes at 23°C,  
another 4 ml  $BBr_3$  solution was added. The reaction  
was stirred for a further 180 minutes. The reaction  
was cooled to -20°C and 15 ml MeOH added. The  
organic phase was washed with  $NaHCO_3$  (aqueous),  
30 dried with  $Na_2SO_4$  and chromatographed on silica  
gel. Hydrolysis of the methyl ester was carried out  
as described in Example 2 to yield 2.2 g of the title  
compound.

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Analysis calculated for  $C_{19}H_{18}O_3ClN$ :

C, 66.37; H, 5.27; N, 4.07; Cl, 10.31

Found: C, 66.54; H, 5.16; N, 3.85; Cl, 10.65.

5

EXAMPLE 24

3-[1-p-Chlorobenzyl-5-acetoxy-3-methylindol-2-yl]-  
propionic acid

10

Using the title compound of Example 23 as starting material, (1 g) was dissolved in  $CH_2Cl_2$  (20 ml) at 0°C and 1 ml pyridine added. 1.8 g acetic anhydride was added and the reaction let stir at 23° for 16 hours. The organic phase was washed with  $H_2O$  (5 X 5 ml), evaporated and chromatographed.

15

Analysis calculated for  $C_{21}H_{20}O_3NCl$ :

Calc.: C, 65.37; H, 5.22; N, 3.63; Cl, 9.19

Found: C, 65.35; H, 5.09; N, 3.54; Cl, 9.25.

EXAMPLE 25

20

3-[4,6-dichloro-1-(4-chlorobenzyl)-3-methyl-1H-indol-2-yl] propanoic acid

25

Following the method of Example 2, but using 1-[1-(chlorophenyl)methyl-1-(3,5-dichlorophenyl)hydrazine hydrochloride and methyl 4-oxohexanoate as the starting materials, in t-butanol as solvent, the title compound was prepared.

Analysis calculated for  $C_{19}H_{16}NCl_3O_2$

C	H	
57.52	4.06	Calc.
57.40	4.20	Found

30

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EXAMPLE 26

3-[1-(4-chlorobenzyl)-4-methoxy-3-methyl-1H-indol-2-yl] propanoic acid

Following the method of Example 2, but using  
5 1-[4-(chlorobenzyl)-1-(3-methoxy phenyl) hydrazine  
hydrochloride and methyl-4-oxohexanoate as the  
starting materials in t-butanol as solvent, the title  
compound was prepared, m.p. 145°C.

Analysis calculated for  $C_{20}H_{20}O_3NCl$ :

10 Calc.: C, 67.12; H, 5.63

Found: C, 67.40; H, 5.43.

EXAMPLE 27

15 1-[1-(4-chlorobenzyl)-3-methyl-5-fluoroindol-2-yl]-  
methoxy acetic acid

Step 1. Methyl 1-(4-chlorobenzyl)-5-fluoro-3-methyl-  
indol-2-carboxylate

Following the procedure of Example 42 Step  
1, but using 1-(4-chlorobenzyl)-1-(4-fluorophenyl)-  
20 hydrazine in place of 1-(4-chlorobenzyl)-1-(4-  
methoxyphenyl)hydrazine, there was obtained the title  
compound of Step 1.

Step 2. 1-[1-(4-chlorobenzyl)-3-methyl-5-fluoroindol-  
25 2-yl]methanol

1.50 g 1-(4-chlorobenzyl)-3-methyl-5-fluoro-  
1H-indole-2-carboxylate Me ester was dissolved in 50  
ml dry THF. Diisobutyl aluminum hydride (1.5 M) in  
tetrahydrofuran (THF) (2 equivalents) was added at  
30 -78°C. The reaction was stirred for 16 hrs., allowed  
to reach room temperature and quenched with  $NH_4Cl$   
(aq.). The organic phase was separated, dried

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( $\text{Na}_2\text{SO}_4$ ) and evaporated to produce 1.32 g of product which was purified on column chromatography to yield the title compound of Step 2.

5    Step 3. The title compound from Step 2 (1.0 g) was dissolved in dry dimethylformamide (DMF) (10 ml) at  $-20^\circ\text{C}$ . Potassium hexamethyl disilazane base in toluene (0.69 M) was added (1.1 molar equivalents) and the reaction stored for 1 hr. Ethyl 2-bromo  
10    acetate (580 mg) (1.2 equivalents) was added and the reaction stirred for 16 h at  $21^\circ\text{C}$ . Water was added (3 ml). The product was isolated after extraction from the aqueous DMF with ether. Following purification on column chromatography, the title ethyl ester was  
15    hydrolysed in 3N NaOH according to the procedure in Example 2.

M.P. =  $154^\circ$

#### EXAMPLE 28

20    3-[1-(4-bromobenzyl)-3-methyl-5-methoxyindol-2-yl]-  
2,2-dimethylpropanoic acid

Following the method of Example 2, but using 1-[4-bromobenzyl]-1-(4-methoxy phenyl) hydrazine hydrochloride and methyl-2,2-dimethyl-4-oxohexanoate  
25    as the starting materials, using t-butanol as the solvent, the title compound was prepared.

M.P. =  $170^\circ$

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EXAMPLE 29

3-[1-(4-chlorobenzyl)-3-methyl-5-methoxyindol-2-yl]  
2-methyl propanoic acid

---

Following the method of Example 2, but using  
5 1-[4-chlorobenzyl]-1-(4-chlorophenyl) hydrazine  
hydrochloride and methyl-3-methyl-4-oxohexanoate as  
starting materials, using t-butanol as solvent, the  
title compound was prepared.

M.P. = 128°

10

EXAMPLE 30

3-[1-(4-iodobenzyl)-3-methyl-5-methoxyindol-2-yl]-2,2-  
dimethyl propanoic acid

---

Following the method of Example 2, but using  
15 1-[4-iodobenzyl]-1-(4-methoxyphenyl)hydrazine  
hydrochloride and methyl-2,2-dimethyl-4-oxo-hexanoate  
as starting materials, using t-butanol as solvent,  
the title compound was prepared.

M.P. = 152°

20

EXAMPLE 31

3-[1-(4-chlorobenzyl)-3-methyl-5-methoxyindol-2-yl]-  
2,2-dimethyl propanol

---

700 mg of 3-[1-(4-chlorobenzyl)-3-methyl-  
25 5-methoxyindol-2-yl]-2,2-dimethyl propanoic acid  
methyl ester was dissolved in 20 ml dry tetrahydro-  
furan. The reaction was cooled to -78°C and 2  
equivalents di-isobutyl aluminium hydride (DIBAL) in  
THF was added. The reaction was allowed to warm to  
30 room temperature and quenched with  $\text{NH}_4\text{Cl}$  (aq.).  
Ethyl acetate was added (75 ml) and the organic phase

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separated, dried and evaporated. The product was isolated by column chromatography.

M.P. = 100.1°

5

EXAMPLE 32

3-[1-(4-chlorobenzyl)-3-methoxy-5-hydroxyindol-2-yl]-  
2,2-dimethyl propanoic acid

Following the method of Example 23, but using the product of Example 22 as starting material, the  
10 title compound was prepared.

M.P. = 137°

EXAMPLE 33

3-[1-(4-chlorobenzyl)-3-methyl-5-methoxyindol-2-yl]-  
15 propanol

Following the method of Example 31, but using the starting material of Example 23, the title compound was prepared.

M.P. = 118°

20

EXAMPLE 34

3-[1-(4-chlorobenzyl)-3-methyl-5-fluoroindol-2-yl]-  
2,2-dimethyl propanoic acid

Following the method of Example 2, but using  
25 1-[4-chlorobenzyl]-1-(4-fluorophenyl)hydrazine hydrochloride 1.9 g and 2,2-dimethyl-4-oxohexanoic acid (950 mg) as starting materials, in t-butanol as solvent, after 16 hrs. at reflux, the solvent was removed in vacuo, and the title compound was isolated  
30 by crystallization and filtration, followed by crystallization from hot ethyl acetate:hexane 9:1.



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Analysis for  $C_{21}H_{21}NO_2ClF$

C	H	
67.47	5.62	Calc.
67.53	5.70	Found

5 M.P. = 124°

EXAMPLE 35

3-[1-(4-chlorobenzyl)-3-methyl-5-fluoroindol-2-yl]-3-methyl propanoic acid

10 Following the method of Example 2, but using 1-[4-chlorobenzyl]-1-(4-fluorophenyl) hydrazine hydrochloride and methyl 3-methyl-4-oxohexanoate as starting materials, the title compound was prepared.

M.P. = 143°

15

EXAMPLE 36

3-[1-(4-chlorobenzyl)-3-methyl-5-hydroxyindol-2-yl] butanoic acid

20 Following the method of Example 23, but using the product of Example 19 as starting material, the title compound was prepared.

M.P. = 162°

EXAMPLE 37

25 Methyl 4-[1-(4-chlorobenzyl)-3-methyl-5-fluoroindol-2-yl]-butanoate

Following the method of Example 44, but using the product of Example 16 as starting materials, the title compound was prepared.

30 Analysis for  $C_{21}H_{21}NO_2FCl$

C	H	
67.47	5.62	Calc.
67.53	5.70	Found

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EXAMPLE 383-[1-(4-chlorobenzyl)-3-methyl-4-propyl-5-hydroxyindol-2-yl]-propanoic acid

210 mg of the methyl ester of Example 39 was  
 5 heated in a Kugelrohr vacuum distillation apparatus  
 at 200°C without vacuum for 90 min. The product was  
 then distilled in vacuo at 0.1 mm Hg, 200°C. The  
 liquid obtained was chromatographed on a preparative  
 plate (hexane 8, ethyl acetate 2). 125 mg. of  
 10 3-[1-(4-chlorobenzyl)-3-methyl-4-(3-propyl)-5-hydroxy-  
 indol-2-yl]propanoic acid methyl ester was isolated,  
 which was then hydrogenated with 10% palladium on  
 charcoal in 10 ml of MeOH with 40 psi H<sub>2</sub> for 3  
 min. The methyl ester title compound was isolated  
 15 from a preparative plate (SiO<sub>2</sub>) (hexane 8, ethyl  
 acetate 2) (82 mg) and the corresponding acid was  
 obtained from hydrolysis as shown in Example 2.

Analysis calculated for C<sub>22</sub>H<sub>24</sub>O<sub>3</sub>NCl +  
 2H<sub>2</sub>O

20	C	H	
	62.43	6.06	Calc.
	62.62	5.73	Found

EXAMPLE 393-[1-(4-chlorobenzyl)-3-methyl-5-prop-2-enoxyindol-2-yl]-propanoic acid

Using 845 mg of the product of Example 23 as  
 starting material, diluted in 23 ml of dimethyl  
 ketone, 476 mg of potassium carbonate and 225 µl of  
 30 allyl bromine was added. The reaction was refluxed  
 overnight. The reaction was then diluted with water  
 and the acetone removed in vacuo. Then the reaction

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was extracted with  $\text{CH}_3\text{CO}_2\text{Et}$  and the organic phase was dried and concentrated to yield after flash chromatography (hexane 8, ethyl acetate 2) 790 mg of the compound, which was then hydrolyzed following the procedure of Example 2.

Analysis calculated for  $\text{C}_{22}\text{H}_{22}\text{O}_3\text{NCl}$

C	H	
68.83	5.77	Calc.
68.88	5.89	Found

M.P. = 131.2°

#### EXAMPLE 40

Methyl-3-[1-(4-chlorobenzyl)-3-methyl-5-methoxyindol-2-yl]-2,2-dimethyl-propanoate

Following the method of Example 45, but using the product of Example 22 as starting material, the title compound was prepared.

M.P. = 110°

#### EXAMPLE 41

3-[1-(4-chlorobenzyl)-3-methyl-5-fluoroindol-2-yl]-2-methyl-butanoic acid

Step 1. Ethyl 2,3-dimethyl-4-oxo-hexanoate

To 4.23 g ethyl 2-bromopropionate in 50 ml acetonitrile was added 2.5 g N-[3-(pent-2-enyl)]-pyrrolidine. The reaction was refluxed for 16 hr. The solvent was removed in vacuo and the product was isolated by chromatography on silica gel to yield 1.5 g of the title compound which was used as such in the second step.

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Step 2. Following the method of Example 2, but using  
1-[4-chlorobenzyl]-1-(4-fluorophenyl)hydrazine  
hydrochloride and ethyl 2,3-dimethyl-4-oxo-  
hexanoate as starting materials, the title compound  
5 was prepared.

M.P. = 177°

#### EXAMPLE 42

1-(4-chlorobenzyl)-3-methyl-5-methoxy-1H-indole-2-  
10 methoxy acetic acid.

Step 1. Methyl 1-(4-chlorobenzyl)-5-methoxy-3-methyl-  
indol-2-carboxylate

To a solution of 1 g 2-keto butyric acid in  
35 ml MeOH (to which had previously been added 1 ml  
15  $\text{CH}_3\text{COCl}$  at 0°C) was added 12.82 g N-benzyl-4-  
methoxyphenyl hydrazine hydrochloride. The solution  
was refluxed for 1 hr., the methanol distilled off  
and a crystalline pasty residue triturated with  
methanol to give 2.6 g crystalline material. The  
20 crystals were swished with 9:1 hexane:EtOAc overnight  
to yield 2.0 g pure product, which was used as such  
in the next step.

Step 2. 1-(4-chlorobenzyl)-3-methyl-5-methoxy-1H-  
25 indole-2-methanol.

1.50 g 1-(4-chlorobenzyl)-3-methyl-5-methoxy-  
1H-indole-2-carboxylate methyl ester was dissolved in  
50 ml dry THF. Diisobutyl aluminum hydride (1.5 M)  
in THF (2 equivalents) was added at -78°C. The  
30 reaction was stirred for 16 hrs., allowed to reach  
room temperature and quenched with  $\text{NH}_4\text{Cl}$  (aq.).  
The organic phase was separated, dried ( $\text{Na}_2\text{SO}_4$ )

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and evaporated to produce 1.32 g of product which was purified on column chromatography to yield the title compound of Step 2.

- 5    Step 3. The product from Step 2 above (1.0 g) was dissolved in dry DMF (10 ml) at -20°C. Potassium hexamethyl disilazane base in toluene (0.69 M) was added (1.1 molar equivalents) and the reaction stirred for 1 hr. Ethyl 2-bromo acetate (580 mg) = 1.2  
10 equivalents was added and the reaction stirred for 16 h at 21°C. Water was added (3 ml). The product was isolated after extraction from the aqueous DMF with ether. Following purification on column chromatography, the title ethyl ester was hydrolysed in 3N  
15 NaOH according to the procedure in Example 2.

M.P. = 128°

#### EXAMPLE 43

- 3-[1-(4-chlorobenzyl)-3-methyl-5-chloroindol-2-yl]-  
20 2,2-dimethyl-propanoic acid

- Following the method of Example 2, but using 1-[4-chlorobenzyl]-1-[4-chlorophenyl]hydrazine hydrochloride and methyl-2,2-dimethyl-4-oxohexanoate in t-butanol as solvent, the title compound was  
25 prepared.

M.P. = 142.5°

#### EXAMPLE 44

- Methyl-3-[-1-(4-chlorobenzyl)-5-methoxy-3-methyl-1H-  
30 indol-2-yl] propanoate

3-[1-(4-chlorobenzyl)-5-methoxy-3-methyl-1H-indol-2-yl] propanoic acid (50 g) was dissolved in

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400 ml absolute methanol and cooled to 0°C. Boron trifluoride etherate (50 ml) was added slowly over 25 min. The reaction was quenched after 16 hr. by the addition of water/ $\text{NaHCO}_3$ . Upon evaporation, the  
 5 water was removed by extraction with  $\text{CH}_2\text{Cl}_2$ . The organic phase was dried and concentrated to yield 47 g of the title methyl ester.

Analysis calculated for  $\text{C}_{20}\text{H}_{21}\text{NO}_3\text{Cl}$ :

	C	H	N	Cl
10 Calc.:	67.83	5.96	3.77	9.53
Found:	67.67	5.21	3.68	9.68

#### EXAMPLE 45

3-[1-(4-aminobenzyl)-5-methoxy-3-methyl-1H-indol-2-yl]-2,2-dimethyl propanoic acid

15 Step 1. 3-[1-(4-nitrobenzyl)-5-methoxy-3-methyl-1H-indol-2-yl]-2,2-dimethyl propanoic acid

Following the method of Example 2, but using 1-[(4-nitrophenyl)methyl-1-(4-methoxyphenyl) hydrazine  
 20 hydrochloride and methyl 2,2-dimethyl-4-oxo-hexanoate as the starting materials and tert-butanol as the solvent, the title compound was prepared.

Analysis calculated for  $\text{C}_{22}\text{H}_{24}\text{O}_5$

	C	H	N
25 Calc.:	66.67	6.06	7.07
Found:	67.00	6.12	7.10

Step 2. 500 mg of the product of Step 1 was dissolved in 35 ml of absolute ethanol and 50 mg of  
 30 10% palladium on carbon catalyst added. The suspension was hydrogenated at 50 psi until consumption of 2 mole equivalents of hydrogen occurred. The

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catalyst was removed by filtration and the title compound was isolated by vacuum distillation of the solvent (489 mg).

M.P. = 173°

5

#### EXAMPLE 46

4-[1-(4-chlorobenzyl)-5-methoxy-3-methyl-1H-indol-2-yl]-2,2-dimethyl butanoic acid

Following the method of Example 2, but using 1-[(4-chlorobenzyl)-1-(4-methoxyphenyl)] hydrazine hydrochloride and methyl 2,2-dimethyl-5-oxoheptanoate as starting materials, the title compound was prepared.

	Analysis calculated for $C_{23}H_{25}NO_3Cl$		
15	C	H	N
	Calc.: 69.28	6.52	3.51
	Found: 69.21	6.93	3.22

#### EXAMPLE 47

4-[1-(4-chlorobenzyl)-5-fluoro-3-methyl-1H-indol-2-yl]-2,2-dimethyl butanoic acid

Following the method of Example 2, but using 1-[4-chlorobenzyl]-1-[4-fluorophenyl] hydrazine hydrochloride and methyl-2,2-dimethyl-5-oxoheptanoate as starting materials, in t-butanol as solvent, the title compound was prepared.

	Analysis calculated for $C_{22}H_{23}NO_2ClF$		
	C	H	N
	Calc.: 68.13	5.60	3.61
30	Found: 68.34	5.69	3.41

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EXAMPLE 48

4-[1-(4-chlorobenzyl)-5-hydroxy-3-methyl-1H-indol-2-yl]-3-methyl butanoic acid

5 Following the method of Example 23, but using 4-[1-(4-chlorobenzyl)-5-methoxy-3-methyl-1H-indol-2-yl]-3-methyl butanoic acid as starting material, the title compound was prepared.

Analysis calculated for  $C_{21}H_{22}NO_3Cl$

	C	H	N	
10	67.13	5.92	3.76	Calc.
	68.36	5.69	3.51	Found

EXAMPLE 49

15 4-[1-(4-methylthiobenzyl)-5-methoxy-3-methyl-1H-indol-2-yl]-3-methyl butanoic acid

Following the method of Example 2, but using 1-[4-methylthiobenzyl]-1-[4-methoxyphenyl] hydrazine hydrochloride and methyl-3-methyl-5-oxoheptanoate as starting materials, in t-butanol as solvent, the title compound was prepared

Analysis calculated for  $C_{21}H_{27}NO_3S$

	C	H	N	
20	69.56	6.92	3.52	Calc.
	69.85	7.20	3.50	Found

25

EXAMPLE 50

3-[1-(4-chlorobenzyl)-5-hydroxy-3-methyl-1H-indol-2-yl]-2,2-dimethyl propanoic acid

30 Following the method of Example 23, but using 3-[1-(4-chlorobenzyl)-5-methoxy-3-methyl-1H-indol-2-yl]-2,2-dimethyl propanoic acid as starting material, the title compound was prepared.

M.P. = 110° (decomposition)



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EXAMPLE 51

3-[1-(4-chlorobenzyl)-5-hydroxy-3-methyl-1H-indol-2-yl]-3-methyl propanoic acid

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5       Following the method of Example 23, but using 3-[1-(4-chlorobenzyl)-5-methoxy-3-methyl-1H-indol-2-yl]-3-methyl propanoic acid as starting material, the title compound was prepared.

	$C_{20}H_{20}NO_3Cl$			
	C	H	N	
10	67.13	5.59	3.9	Calc.
	67.22	5.74	3.97	Found

EXAMPLE 52

15       3-[1-(4-chlorobenzyl)-5-ethoxy-3-methyl-1H-indol-2-yl]-2,2-dimethyl propanoic acid

---

      The title compound of Example 50 was treated according to the method described in Example 39 using ethyl bromide as the alkylating agent. The product was isolated by chromatography on silica gel

20       (CH<sub>2</sub>Cl<sub>2</sub>)..

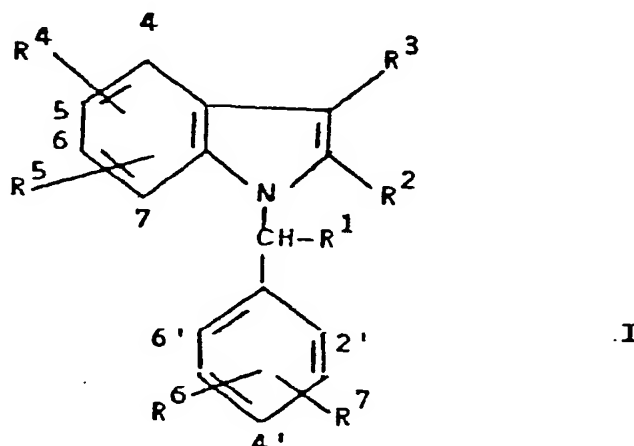
      M.P. = 148°

25

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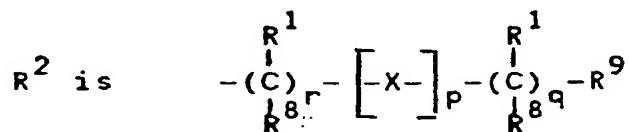
CLAIMS

1. A pharmaceutical composition useful as a prostaglandin antagonist in mammals comprising a prostaglandin antagonizing amount of compound of the Formula I or a compound that is a pharmaceutically acceptable salt thereof:



where

$R^1$  is H or alkyl of 1 to 6 carbons or  $R^1$  and  $R^8$  taken together form a group  $(CH_2)_v$  wherein  $v$  is 1 to 7;



where

each  $R^8$  is independently H, OH,  $C_1$  to  $C_4$ -O-alkyl or alkyl of 1 to 4 carbons; or an  $R^1$  and an  $R^8$  taken together form a group  $(CH_2)_v$  wherein  $v$  is 1 to 7.

$R^9$  is  $\text{COOR}^1$ ;  $\text{CH}_2\text{OH}$ ;  $\text{CHO}$ ; tetrazole;  
 $\text{NHSO}_2\text{R}^{10}$  wherein  $\text{R}^{10}$  is  $\text{OH}$ , alkyl or alkoxy of  
 1 to 6 carbons, perhaloalkyl of 1 to 6 carbons,  
 phenyl or phenyl substituted by alkyl or alkoxy  
 5 groups of 1 to 3 carbons, halogen, hydroxy,  $\text{COOH}$ ,  $\text{CN}$ ,  
 formyl or acyl to 1 to 6 carbons;  $\text{CONHSO}_2\text{R}^{10}$ ;  
 hydroxymethylketone;  $\text{CN}$ ; or  $\text{CON}(\text{R}^8)_2$ ;  
 $\text{X}$  is  $\text{O}$ ;  $\text{S}$ ;  $\text{SO}$ ;  $\text{SO}_2$ ;  $\text{NR}^{11}$  wherein  $\text{R}^{11}$   
 is  $\text{H}$ , alkyl of 1 to 6 carbons, acyl of 1 to 6 carbons,  
 10  $\text{CN}$ ;  $\text{CR}^1\text{R}^8$ ;

or the unit  $\begin{array}{c} \text{R}^1 \quad \text{R}^8 \\ | \quad | \\ -\text{C} \cdots \text{C}- \end{array}$  wherein the dotted line  
 represents an optional triple bond and in which the  
 $\text{R}^1$  and  $\text{R}^8$  substituents are absent when a triple  
 15 bond is present;

$r$  and  $q$  are each independently 0 to 5 and  $p$   
 is 0 or 1 provided that the total of  $p$ ,  $q$  and  $r$  is 2  
 to 6;

$\text{R}^3$  is  $\text{H}$ , alkyl of 1 to 6 carbons; phenyl  
 20 or phenyl substituted by  $\text{R}^4$ ; or  $\text{C}_1$  to  $\text{C}_4$  alkyl-  
 phenyl or  $\text{C}_1$  to  $\text{C}_4$  alkylphenyl in which the  
 phenyl is substituted by  $\text{R}^4$ ;

$\text{R}^4$ ,  $\text{R}^5$ ,  $\text{R}^6$  and  $\text{R}^7$  are each  
 independently selected from:

- 25 (1) hydrogen;  
 (2) alkyl having 1 to 6 carbon atoms;  
 (3) alkenyl having 2 to 6 carbon atoms;  
 (4)  $-(\text{CH}_2)_n\text{M}$   
 wherein  $n$  is 0 to 3 and  $\text{M}$  is  
 30 a)  $\text{OR}^{12}$ ;  
 b) halogen;  
 c)  $\text{CF}_3$ ;

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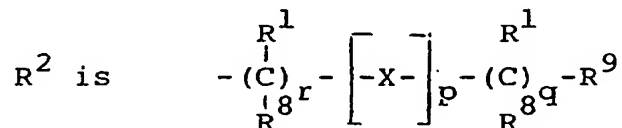
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- 5
- d)  $SR^{12}$ ;
- e) phenyl or substituted phenyl  
wherein substituted phenyl is  
as defined below in the  
definition of  $R^{12}$ ;
- f)  $COOR^{13}$ ;
- g)  $\begin{array}{c} O \\ || \\ C-R^{14} \end{array}$ ;
- h) tetrazole;
- 10
- i)  $\begin{array}{c} O \\ || \\ -NH-C-R^{15} \end{array}$  wherein  $R^{15}$  is  
 $C_1$  to  $C_6$  alkyl, benzyl or  
phenyl;
- j)  $-NR^{13}R^{13}$ ;
- 15
- k)  $-NHSO_2R^{16}$  wherein  $R^{16}$   
is  $C_1$  to  $C_6$  alkyl,  
phenyl, or  $CF_3$ ;
- l)  $\begin{array}{c} O \\ || \\ -C-CH_2OH \end{array}$ ;
- 20
- m)  $-SOR^{12}$ ;
- n)  $-CONR^{13}R^{13}$ ;
- o)  $-SO_2NR^{13}R^{13}$ ;
- p)  $-SO_2R^{12}$ ;
- 25
- q)  $NO_2$ ;
- r)  $\begin{array}{c} O \\ || \\ O-C-R^{14} \end{array}$ ;
- s)  $\begin{array}{c} O \\ || \\ O-C-NR^{13}R^{13} \end{array}$ ;
- 30
- t)  $\begin{array}{c} O \\ || \\ O-C-OR^{15} \end{array}$ ;
- u)  $CN$ ;

each  $R^{12}$  independently is H;  $C_1$  to  $C_6$  alkyl; benzyl; phenyl or substituted phenyl wherein the substituents are  $C_1$  to  $C_3$  alkyl, halogen, CN,  $CF_3$ ,  $COOR^{13}$ ,  $CH_2COOR^{13}$ ,  $C_1$  to  $C_3$  alkoxy, or  $C_1$  to  $C_4$  perfluoroalkyl;  
 5 each  $R^{13}$  is independently H, phenyl or  $C_1$  to  $C_6$  alkyl; and,  
 each  $R^{14}$  independently is H,  $(CH_2)_n COOR^{13}$  wherein n is 0 to 4,  $C_1$  to  $C_6$  alkyl,  $CF_3$ ,  
 10 phenyl, or substituted phenyl wherein substituted phenyl is as defined above in the definition of  $R^{12}$ ; and a pharmaceutically acceptable carrier.

2. A composition according to Claim 1,  
 15 wherein:  
 $R^1$  is H or alkyl of 1 to 3 carbons or  $R^1$  and  $R^8$  taken together form a group  $(CH_2)_{v_1}$  wherein v is 1 to 7, with the proviso that  $R^1$  on the benzylic carbon attached to the indole nitrogen  
 20 is H;



wherein:  
 25 each  $R^8$  is independently H, or alkyl of 1 to 4 carbons; or an  $R^1$  and an  $R^8$  taken together form a group  $(CH_2)_{v_1}$  wherein v is 1 to 7.  
 $R^9$  is  $COOR^1$ ;  $CH_2OH$ ;  $CHO$ ; or tetrazole;  
 X is O; S;  $SO$ ;  $SO_2$ ;  $NR^{11}$  wherein  $R^{11}$   
 30 is H, alkyl of 1 to 6 carbons, acyl of 1 to 6 carbons, CN;  $CR^1R^8$ ;

or the unit  $\begin{array}{c} R^1 \quad R^8 \\ | \quad | \\ -C \equiv C- \end{array}$  wherein the dotted line represents an optional triple bond and in which the  $R^1$  and  $R^8$  substituents are absent when a triple

5 bond is present;

$r$  and  $q$  are each independently 0 to 5 and  $p$  is 0 or 1 provided that the total of  $p$ ,  $q$  and  $r$  is 2 to 3;

10  $R^3$  is alkyl of 1 to 6 carbons, but is not cycloalkyl;

$R^4$ ,  $R^5$ ,  $R^6$  and  $R^7$  are each independently selected from:

- (1) hydrogen;
- (2) alkyl having 1 to 6 carbon atoms;
- 15 (3) M wherein M is
  - a)  $OR^{12}$ ;
  - b) halogen;
  - c)  $CF_3$ ;
  - 20 d)  $SR^{12}$ ;
  - e)  $-SOR^{12}$ ;
  - f)  $-SO_2R^{12}$ ;
  - 25 g)  $O-\overset{\overset{O}{\parallel}}{C}-R^{14}$  wherein  $R^{14}$  is H,  $(CH_2)_nCOOR^{13}$  wherein  $n$  is 0 to 4,  $C_1$  to  $C_6$  alkyl,  $CF_3$ , phenyl, or substituted phenyl wherein substituted phenyl is as defined above in the definition of  $R^{12}$ ; H,  $C_1$  to  $C_6$  alkyl,  $CF_3$ , phenyl
  - 30

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or substituted phenyl wherein  
substituted phenyl is as  
defined below in the  
definition of  $R^{12}$ ;

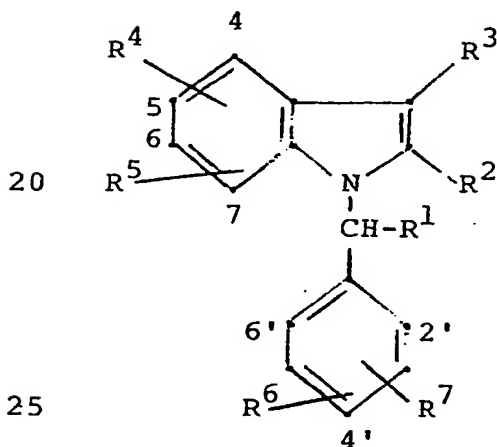
5

h) CN;

each  $R^{12}$  is independently H;  $C_1$  to  $C_6$   
alkyl; benzyl; phenyl or substituted phenyl wherein  
the substituents are  $C_1$  to  $C_3$  alkyl, halogen, CN,  
 $CF_3$ ,  $COOR^{13}$ ,  $CH_2COOR^{13}$ , wherein  $R^{13}$  is H,  
10 phenyl;  $C_1$  to  $C_6$  alkyl or  $C_1$  to  $C_4$  perfluoroalkyl;  
or a pharmaceutically acceptable salt thereof, and a  
pharmaceutically acceptable carrier.

### 3. A compound of the Formula Ia:

15

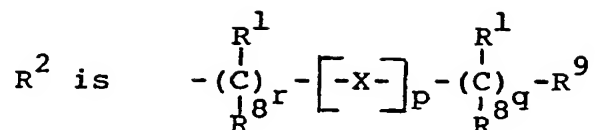


Ia

25

wherein:

$R^1$  is H or alkyl of 1 to 6 carbons or  $R^1$  and  
30  $R^8$  taken together form a group  $(CH_2)_v$   
wherein  $v$  is 1 to 7;



wherein:

- 5 each  $R^8$  is independently H, OH,  $C_1$  to  $C_4$ -O-alkyl, or alkyl of 1 to 4 carbons or  $R^1$  and  $R^8$  taken together form a group  $(CH_2)_v$  wherein v is 1 to 7;
- 10  $R^9$  is  $COOR^1$ ;  $CH_2OH$ ; CHO; tetrazole;  $NHSO_2R^{10}$  wherein  $R^{10}$  is OH, alkyl or alkoxy of 1 to 6 carbons, perhaloalkyl of 1 to 6 carbons, phenyl or phenyl substituted by alkyl or alkoxy groups of 1 to 3 carbons, halogen, hydroxy, COOH, CN, formyl or acyl to 1 to 6 carbons;  $CONHSO_2R^{10}$ ;
- 15 hydroxymethylketone; CN; or  $CON(R^8)_2$ ;  
 $X$  is O; S;  $SO$ ;  $SO_2$ ;  $NR^{11}$  wherein  $R^{11}$  is H, alkyl of 1 to 6 carbons, acyl of 1 to 6 carbons, CN;  $CR^1R^8$ ;
- 20 or the unit  $\begin{array}{c} R^1 \quad R^8 \\ | \quad | \\ -C \equiv C- \end{array}$  wherein the dotted line represents an optional triple bond and in which the  $R^1$  and  $R^8$  substituents are absent when a triple bond is present;
- 25  $r$  and  $q$  are each independently 0 to 5 and  $p$  is 0 or 1 provided that the total of  $p$ ,  $q$  and  $r$  is 2 to 6, with the proviso that when  $R^1$  and  $R^8$  are H,  $X$  is  $CH_2$ ,  $R^4$  is 5-methoxy and  $R^6$  is halogen, then the sums of  $p$ ,  $q$  and  $r$  is 3 to 6;
- 30  $R^3$  is H, alkyl of 1 to 6 carbons; phenyl or phenyl substituted by  $R^4$ ; or  $C_1$  to  $C_4$  alkyl-



phenyl or  $C_1$  to  $C_4$  alkylphenyl in which the phenyl is substituted by  $R^4$ ;

$R^4$ ,  $R^5$ ,  $R^6$  and  $R^7$  are each independently selected from:

- 5 (1) hydrogen;
- (2) alkyl having 1 to 6 carbon atoms;
- (3) alkenyl having 2 to 6 carbon atoms;
- (4)  $-(CH_2)_nM$ 
  - 10 a)  $OR^{12}$ ;
  - b) halogen;
  - c)  $CF_3$ ;
  - d)  $SR^{12}$ ;
  - 15 e) phenyl or substituted phenyl wherein substituted phenyl is as defined below in the definition of  $R^{12}$ ;
  - f)  $COOR^{13}$ ;
  - 20 g)  $\begin{array}{c} O \\ || \\ C-R^{14} \end{array}$ ;
  - h) tetrazole;
  - i)  $-NH-\begin{array}{c} O \\ || \\ C \end{array}-R^{15}$  wherein  $R^{15}$  is
    - 25  $C_1$  to  $C_6$  alkyl, benzyl or phenyl;
    - j)  $-NR^{13}R^{13}$ ;
    - k)  $-NHSO_2R^{16}$  wherein  $R^{16}$  is  $C_1$  to  $C_6$  alkyl, phenyl, or  $CF_3$ ;
    - 30 l)  $\begin{array}{c} O \\ || \\ -C-CH_2OH \end{array}$ ;

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- 5 m)  $-\text{SOR}^{12};$   
 n)  $-\text{CONR}^{13}\text{R}^{13};$   
 o)  $-\text{SO}_2\text{NR}^{13}\text{R}^{13};$   
 p)  $-\text{SO}_2\text{R}^{12};$   
 q)  $\text{NO}_2;$   
 r)  $\text{O}-\overset{\text{O}}{\underset{\text{||}}{\text{C}}}-\text{R}^{14};$   
 s)  $\text{O}-\overset{\text{O}}{\underset{\text{||}}{\text{C}}}-\text{NR}^{13}\text{R}^{13};$   
 10 t)  $\text{O}-\overset{\text{O}}{\underset{\text{||}}{\text{C}}}-\text{OR}^{15};$   
 u)  $\text{CN};$

each  $\text{R}^{12}$  is independently H;  $\text{C}_1$  to  $\text{C}_6$  alkyl; benzyl; phenyl or substituted phenyl wherein the substituents are  $\text{C}_1$  to  $\text{C}_3$  alkyl, halogen, CN,  $\text{CF}_3$ ,  $\text{COOR}^{13}$ ,  $\text{CH}_2\text{COOR}^{13}$   $\text{C}_1$  to  $\text{C}_3$  alkoxy, or  $\text{C}_1$  to  $\text{C}_4$  perfluoroalkyl;

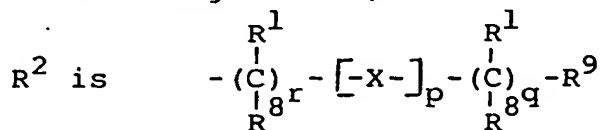
each  $\text{R}^{13}$  is independently H, phenyl or  $\text{C}_1$  to  $\text{C}_6$  alkyl;  
 20 each  $\text{R}^{14}$  is independently H,  $(\text{CH}_2)_n\text{COOR}^{13}$  wherein n is 0 to 4,  $\text{C}_1$  to  $\text{C}_6$  alkyl,  $\text{CF}_3$ , phenyl, or substituted phenyl wherein substituted phenyl is as defined above in the definition of  $\text{R}^{12}$ ; or a pharmaceutically acceptable salt thereof.

25

4. A compound of Claim 3 wherein:

$\text{R}^1$  is H or alkyl of 1 to 3 carbons, with the proviso that  $\text{R}^1$  on the benzylic carbon attached to the indole nitrogen is H;

30



wherein:

each  $R^8$  is independently H or alkyl of 1 to 4 carbons, with the proviso that at least one of the  $R^1$  or  $R^8$  substituents in  $R^2$  is not hydrogen;

5  $R^9$  is COOH;  $CH_2OH$ ; CHO; or tetrazole;

$X$  is  $CR^1R^8$ ;

$r$  and  $q$  are each independently 0 to 3 and  $p$  is 0 or 1 provided that the total of  $p$ ,  $q$  and  $r$  is 2 to 3;

10  $R^3$  is alkyl of 1 to 6 carbons, but not cycloalkyl;

$R^4$ ,  $R^5$ ,  $R^6$  and  $R^7$  are each independently selected from:

- 15 (1) hydrogen;  
(2) alkyl having 1 to 6 carbon atoms;  
(3) M wherein M is

- a)  $OR^{12}$ ;  
b) halogen;  
c)  $CF_3$ ;

20

- d)  $SR^{12}$ ;  
e)  $-SOR^{12}$ ;  
f)  $-SO_2R^{12}$ ;

25

- g)  $O-\overset{\overset{O}{\parallel}}{C}-R^{14}$ , wherein  $R^{14}$  is H,  $C_1$  to  $C_6$  alkyl,  $CF_3$ , phenyl or substituted phenyl wherein substituted phenyl is as defined below in the definition of  $R^{12}$ ;

30

- h) CN;

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each  $R^{12}$  is independently H;  $C_1$  to  $C_6$  alkyl; or benzyl; or a pharmaceutically acceptable salt thereof.

5                    5. A compound of Claim 3 wherein:  
 $R^1$  is H or alkyl of 1 to 3 carbons, with the proviso that  $R^1$  on the benzylic carbon attached to the indole nitrogen is H;

10                     $R^2$  is 
$$-\underset{\underset{R^8}{|}}{\overset{\overset{R^1}{|}}{(C)}}_r - [-X-]_p - \underset{\underset{R^8}{|}}{\overset{\overset{R^1}{|}}{(C)}}_q - R^9$$

wherein:

each  $R^8$  is independently H or alkyl of 1 to 4 carbons;

15                     $R^9$  is COOH;  $CH_2OH$ ; CHO; or tetrazole;

X is O; S;  $SO$ ; or  $SO_2$ ;

r and q are each independently 0 to 3 and p is 1 provided that the total of p, q and r is 2 to 3;

20                     $R^3$  is alkyl of 1 to 6 carbons, but not cycloalkyl;

$R^4$ ,  $R^5$ ,  $R^6$  and  $R^7$  are each independently selected from:

- (1) hydrogen;
- (2) alkyl having 1 to 6 carbon atoms;
- 25                    (3) M wherein M is
- a)  $OR^{12}$ ;
  - b) halogen;
  - c)  $CF_3$ ;
  - d)  $SR^{12}$ ;
  - e)  $-SOR^{12}$ ;
  - f)  $-SO_2R^{12}$ ;
- 30

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- 5 g)  $\text{O}-\overset{\text{O}}{\underset{\text{||}}{\text{C}}}-\text{R}^{14}$ , wherein  $\text{R}^{14}$  is H,  
 $\text{C}_1$  to  $\text{C}_6$  alkyl,  $\text{CF}_3$ ,  
phenyl or substituted phenyl  
wherein substituted phenyl is  
as defined below in the  
definition of  $\text{R}^{12}$ ;
- h) CN;
- each  $\text{R}^{12}$  is independently H;  $\text{C}_1$  to  $\text{C}_6$   
10 alkyl; or benzyl;  
or a pharmaceutically acceptable salt thereof.

6. The compounds of Claim 3:

- 15 3-[1-(p-Chlorobenzyl)-5-chloro-3-methyl-2-indolyl]-  
propionic acid;
- 3-[1-(p-Chlorobenzyl)-3-methyl-5-fluoro-2-indolyl]-  
propionic acid;
- 3-[1-p-Chlorobenzyl-3-methyl-4,6-dichloro-2-  
indolyl]propionic acid;
- 20 3-[1-(p-Chlorobenzyl)-3-methyl-4-methoxy-2-  
indolyl]propionic acid;
- 3-[1-(p-chlorobenzyl)-3-methyl-6-methoxy-2-  
indolyl]propionic acid;
- 25 3-[1-(p-Chlorobenzyl)-3,4-dimethyl-2-indolylpro-  
pionic acid and 3-[1-(p-chlorobenzyl)-3,6-  
dimethyl-2-indolyl]propionic acid (as a mixture);
- 1-(4-Chlorobenzyl)-3-methyl-5-methoxy-2-(4'-carboxy-  
butyl)indole;
- 3-[1-(p-Chlorobenzyl)-3,5-dimethyl-2-indolyl]-  
30 propionic acid;
- 1-(4-Chlorobenzyl)-3-methyl-5-methoxy-2-(3-carboxy-  
propyl)indole;

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- 3-[1-(p-Chlorobenzyl)-3-methyl-2-indolyl]propionic  
acid;
- 3-[1-(p-Chlorobenzyl)-5-bromo-3-methyl-2-indolyl]-  
propionic acid;
- 5 1-(4-Thiomethylbenzyl)-5-methoxy-3-methyl-2-(2-  
carboxyethyl)indole;
- 1-(4-Thiomethylbenzyl)-5-methoxy-3-methyl-2-(2-  
carboxyethyl)indole S-oxide;
- 1-(4-Thiomethylbenzyl)-5-methoxy-3-methyl-2-(3-  
10 carboxypropyl)indole;
- 4-[1-(p-Chlorobenzyl)-3-methyl-5-fluoro-2-indolyl]-  
butanoic acid;
- 3-[1-(p-Thiomethylbenzyl)-3-methyl-5-fluoro-2-  
indolyl]propanoic acid;
- 15 3-[1-p-Methylsulfoxybenzyl)-3-methyl-5-fluoro-2-  
indolyl]-propanoic acid;
- 3-[1-(4-Chlorobenzyl)-3-methyl-5-methoxy-2-indolyl]-  
butanoic acid;
- 3-Methyl-4-[1-p-chlorobenzyl-5-methoxy-3-methylindol-  
20 2-yl]butanoic acid;
- 3-Methyl-4-[1-p-chlorobenzyl-5-fluoro-3-methylindol-2-  
yl]butanoic acid;
- 3-(1-p-Chlorobenzyl-3-methyl-5-methoxyindol-2-yl)-2,2-  
dimethylpropanoic acid;
- 25 3-[1-p-Chlorobenzyl-5-hydroxy-3-methylindol-2-yl]-  
propionic acid;
- 3-[1-p-Chlorobenzyl-5-acetoxy-3-methylindol-2-yl]-  
propionic acid;
- 3-[4,6-dichloro-1-(4-chlorobenzyl)-3-methyl-1H-  
30 indol-2-yl]propanoic acid;
- 3-[1-(4-chlorobenzyl)-4-methoxy-3-methyl-1H-indol-  
2-yl]propanoic acid;

- 2-[1-(4-chlorobenzyl)-3-methyl-5-fluoroindol-2-yl]methoxylacetic acid;
- 3-[1-(4-bromobenzyl)-3-methyl-5-methoxyindol-2-yl]-2,2-dimethylpropanoic acid;
- 5 3-[1-(4-chlorobenzyl)-3-methyl-5-methoxyindol-2-yl]2-methyl-propanoic acid;
- 3-[1-(4-iodobenzyl)-3-methyl-5-methoxyindol-2-yl]-2,2-dimethyl-propanoic acid;
- 3-[1-(4-chlorobenzyl)-3-methyl-5-methoxyindol-2-yl]-2,2-dimethyl-propanol;
- 10 3-[1-(4-chlorobenzyl)-3-methoxy-5-hydroxyindol-2-yl]-2,2-dimethyl-propanoic acid;
- 3-[1-(4-chlorobenzyl)-3-methyl-5-methoxyindol-2-yl]-propanol;
- 15 3-[1-(4-chlorobenzyl)-3-methyl-5-fluoroindol-2-yl]-2,2-dimethyl propanoic acid;
- 3-[1-(4-chlorobenzyl)-3-methyl-5-fluoroindol-2-yl]-3-methyl-propanoic acid;
- 3-[1-(4-chlorobenzyl)-3-methyl-5-hydroxyindol-2-yl]butanoic acid;
- 20 Methyl 4-[1-(4-chlorobenzyl)-3-methyl-5-fluoroindol-2-yl]-butanoate;
- 3-[1-(4-chlorobenzyl)-3-methyl-4-propyl-5-hydroxyindol-2-yl]-propanoic acid;
- 25 3-[1-(4-chlorobenzyl)-3-methyl-5-prop-2-enoxyindol-2-yl]-propanoic acid;
- 3-[1-(4-chlorobenzyl)-3-methyl-5-methoxyindol-2-yl]-2,2-dimethyl-propanoate;
- 3-[1-(4-chlorobenzyl)-3-methyl-5-fluoroindol-2-yl]-2-methyl-butanoic acid;
- 30 1-(4-chlorobenzyl)-3-methyl-5-methoxy-1H-indole-2-methoxy acetic acid;

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- 3-[1-(4-chlorobenzyl)-3-methyl-5-chloroindol-2-yl]-2,2-dimethyl-propanoic acid;  
methyl-3[1(4-chlorobenzyl)-5-methoxy-3-methyl-1H-indol-2-yl]propanoate;
- 5 3-[1-(4-aminobenzyl)-5-methoxy-3-methyl-1H-indol-2-yl]-2,2-dimethyl propanoic acid;  
4-[1-(4-chlorobenzyl)-5-methoxy-3-methyl-1H-indol-2-yl]-2,2-dimethyl butanoic acid;  
4-[1-(4-chlorobenzyl)-5-fluoro-3-methyl-1H-indol-2-yl]-2,2-dimethyl butanoic acid;
- 10 4-[1-(4-chlorobenzyl)-5-hydroxy-3-methyl-1H-indol-2-yl]-3-methyl butanoic acid;  
3-[1-(4-chlorobenzyl)-5-hydroxy-3-methyl-1H-indol-2-yl]-2,2-dimethyl propanoic acid;
- 15 3-[1-(4-chlorobenzyl)-5-hydroxy-3-methyl-1H-indol-2-yl]-3-methyl propanoic acid;  
3-[1-(4-chlorobenzyl)-5-ethoxy-3-methyl-1H-indol-2-yl]-2,2-dimethyl propanoic acid;
- 20 4-[1-(4-chlorobenzyl-5-fluoro-3-methyl-1H-indol-2-yl)]-2,4,3,3-tetramethyl butanoic acid;  
4-[1-(4-chlorobenzyl-5-fluoro-3-methyl-1H-indol-2-yl)]-4,3,3-trimethyl butanoic acid;  
4-[1-(4-chlorobenzyl-5-fluoro-3-methyl-1H-indol-2-yl)]-2,2,3-trimethyl butanoic acid;
- 25 4-[1-(4-chlorobenzyl-5-fluoro-3-methyl-1H-indol-2-yl)]-2,3,3-trimethyl butanoic acid;  
4-[1-(4-chlorobenzyl-5-methoxy-3-methyl-1H-indol-2-yl)]-2,2,3-trimethyl butanoic acid;
- 30 4-[1-(4-chlorobenzyl-5-ethoxy-3-methyl-1H-indol-2-yl)]-2,2,3-trimethyl butanoic acid;  
4-[1-(4-chlorobenzyl-5-chloro-3-methyl-1H-indol-2-yl)]-2,2,3-trimethyl butanoic acid;



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4-[1-(4-chlorobenzyl)-3-methyl-5-trifluoromethyl-1H-indol-2-yl]-2,4,3,3-tetramethyl butanoic acid;  
4-[1-(4-chlorobenzyl)-3-methyl-5-trifluoromethylthio-1H-indol-2-yl]-2,4,3,3-tetramethyl butanoic acid;  
3-[1-(4-chlorobenzyl)-5-ethoxy-3-methyl-1H-indol-2-yl]-2,2,3-trimethyl propanoic acid;  
3-[1-(4-chlorobenzyl)-5-ethoxy-3-methyl-1H-indol-2-yl]-2,3,3-trimethyl propanoic acid;  
3-[1-(4-chlorobenzyl)-5-ethoxy-3-methyl-1H-indol-2-yl]-2,2,3,3-tetramethyl propanoic acid;  
3-[1-(4-chlorobenzyl)-5-methoxy-3-methyl-1H-indol-2-yl]-2,2,3-trimethyl propanoic acid;  
3-[1-(4-chlorobenzyl)-5-fluoro-3-methyl-1H-indol-2-yl]-2,2,3-trimethyl propanoic acid;  
3-[1-(4-chlorobenzyl)-5-chloro-3-methyl-1H-indol-2-yl]-2,2,3-trimethyl propanoic acid;  
3-(1-p-chlorobenzyl-3-methyl-5-methoxyindol-2-yl)-2,2-diethyl propanoic acid;  
3-[1-(4-chlorobenzyl)-3-methyl-5-fluoroindol-2-yl]-2,2-diethyl propanoic acid;  
3-[1-(4-chlorobenzyl)-3-methyl-5-fluoroindol-2-yl]-2-ethyl propanoic acid;  
3-[1-(4-chlorobenzyl)-3-ethyl-5-fluoroindol-2-yl]-3-methyl propanoic acid; and  
3-[1-(4-chlorobenzyl)-3-methyl-5-methoxy-2-indolyl]pentanoic acid.

7. A composition as claimed in Claim 1 for use in the inhibition of leukotriene synthesis in a mammal.
8. A compound as claimed in Claim 3 for use in the inhibition of leukotriene synthesis in a mammal.
9. A composition as claimed in Claim 1 or 2 that additionally comprises a second active ingredient that is a non-steroidal anti-inflammatory drug; a peripheral analgesic agent; a cyclooxygenase inhibitor; a leukotriene antagonist; a leukotriene biosynthesis inhibitor; an  $H_2$ -receptor antagonist; an antihistaminic agent; a prostaglandin antagonist; an ACE inhibitor, or a thromboxane synthetase inhibitor, in which the weight ratio of the compound of Formula I to the second active ingredient is in the range from 1000:1 to 1:1000.
10. A pharmaceutical composition comprising a compound as claimed in any one of Claims 3 to 6 together with a second active ingredient as defined in Claim 9.

**EUROPEAN PATENT APPLICATION**

Application number: 85304468.3

Int. Cl.<sup>4</sup>: **C 07 D 209/22**  
**A 61 K 31/40**

Date of filing: 24.06.85

Priority: 25.06.84 US 624173

Date of publication of application:  
02.01.86 Bulletin 86/1

Date of deferred publication of search report: 25.06.86

Designated Contracting States:  
AT BE CH DE FR GB IT LI LU NL SE

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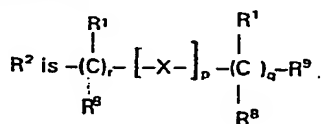
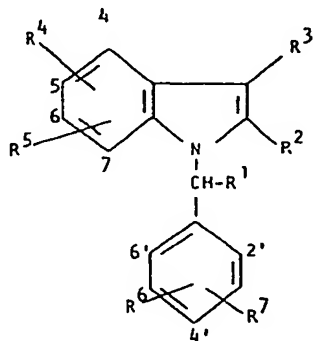
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Indole-2-alkanoic acids and their use as prostaglandin antagonists.

Compounds of the formula I



where

each R<sup>8</sup> is independently H, OH, C<sub>1</sub> to C<sub>4</sub>-O-alkyl or alkyl of 1 to 4 carbons; or an R<sup>1</sup> and an R<sup>8</sup> taken together form a group (CH<sub>2</sub>)<sub>v</sub> wherein v is 1 to 7,

R<sup>9</sup> is COOR<sup>1</sup>; CH<sub>2</sub>OH; CHO; tetrazole; NHSO<sub>2</sub>R<sup>10</sup> wherein R<sup>10</sup> is OH, alkyl or alkoxy of 1 to 6 carbons, perhaloalkyl of 1 to 6 carbons, phenyl or phenyl substituted by alkyl or alkoxy groups of 1 to 3 carbons, halogen, hydroxy, COOH, CN, formyl or acyl to 1 to 6 carbons; CONHS<sub>2</sub>R<sup>10</sup>; hydroxy-methylketone; CN; or CON(R<sup>8</sup>)<sub>2</sub>;

X is O; S; SO; SO<sub>2</sub>; N<sup>11</sup> wherein R<sup>11</sup> is H, alkyl of 1 to 6 carbons, acyl of 1 to 6 carbons, CN, CR<sup>1</sup>R<sup>8</sup>;

or the unit  $\begin{array}{c} R^1 \quad R^8 \\ | \quad | \\ -C \equiv C- \end{array}$  wherein the dotted line represents an optional triple bond and in which the R<sup>1</sup> and R<sup>8</sup> substituents

where

R<sup>1</sup> is H or alkyl of 1 to 6 carbons or R<sup>1</sup> and R<sup>8</sup> taken together form a group (CH<sub>2</sub>)<sub>v</sub> wherein v is 1 to 7;

are absent when a triple bond is present;

r and q are each independently 0 to 5 and p is 0 to 1 provided that the total of p, q and r is 2 to 6;

R<sup>3</sup> is H, alkyl of 1 to 6 carbons; phenyl or phenyl substituted by R<sup>4</sup>; or C<sub>1</sub> to C<sub>4</sub> alkyl-phenyl of C<sub>1</sub> to C<sub>4</sub> alkylphenyl in which the phenyl is substituted by R<sup>4</sup>;

R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup> and R<sup>7</sup> are each independently selected from:

- (1) hydrogen;
- (2) alkyl having 1 to 6 carbon atoms;
- (3) alkenyl having 2 to 6 carbon atoms;
- (4)  $-(CH_2)_nM$

wherein n is 0 to 3 and M is

- a) OR<sup>12</sup>;
- b) halogen;
- c) CF<sub>3</sub>;
- d) SR<sup>12</sup>;
- e) phenyl or substituted phenyl wherein substituted phenyl is as defined below in the definition of R<sup>12</sup>;
- f) COOR<sup>13</sup>;  
O

- g) C-R<sup>14</sup>;
- h) tetrazole;

- i)  $-NH-\overset{\overset{O}{\parallel}}{C}-R^{15}$  wherein R<sup>15</sup> is C<sub>1</sub> to C<sub>6</sub> alkyl, benzyl or phenyl;
- j)  $-NR^{13}R^{13}$ ;
- k)  $-NHSO_2R^{15}$  wherein R<sup>16</sup> is C<sub>1</sub> to C<sub>6</sub> alkyl, phenyl, or CF<sub>3</sub>;  
O

- l)  $-C-CH_2OH$ ;
- m)  $-SOR^{12}$ ;
- n)  $-CONR^{13}R^{13}$ ;
- o)  $-SO_2NR^{13}R^{13}$ ;
- p)  $-SO_2R^{12}$ ;
- q) NO<sub>2</sub>;

- r)  $\overset{\overset{O}{\parallel}}{O}-C-R^{14}$ ;  
O

- s)  $O-C-NR^{13}R^{13}$ ;

- t)  $\overset{\overset{O}{\parallel}}{O}-C-OR^{15}$ ;
- u) CN;

each R<sup>12</sup> independently is H; C<sub>1</sub> to C<sub>6</sub> alkyl; benzyl; phenyl or substituted phenyl wherein the substituents are C<sub>1</sub> to C<sub>3</sub> alkyl, halogen, CN, CF<sub>3</sub>, COOR<sup>13</sup>, CH<sub>2</sub>COOR<sup>13</sup>, C<sub>1</sub> to C<sub>3</sub> alkoxy, or C<sub>1</sub> to C<sub>4</sub> perfluoroalkyl;

each R<sup>13</sup> is independently H, phenyl or C<sub>1</sub> to C<sub>6</sub> alkyl; and,

each R<sup>14</sup> independently is H, (CH<sub>2</sub>)<sub>n</sub>COOR<sup>13</sup> wherein n is 0 to 4, C<sub>1</sub> to C<sub>6</sub> alkyl, CF<sub>3</sub>, phenyl, or substituted phenyl wherein substituted phenyl is as defined above in the definition of R<sup>12</sup>; and their pharmaceutically acceptable salts are useful as prostaglandin antagonists and are made into pharmaceutical compositions. Certain of the compounds are novel.



European Patent  
Office

# EUROPEAN SEARCH REPORT

0166591  
Application number

EP 85 30 4468

## DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int Cl 4)
Y	CH-A- 455 777 (GEIGY AG) * Whole document *	1	C 07 D 209/22 A 61 K 31/40
Y	--- CH-A- 454 858 (GEIGY AG) * Whole document *	1	
Y	--- JOURNAL OF MEDICINAL CHEMISTRY, vol. 11, no. 6, 25th October 1968, pages 1252-1255, American Chemical Society, US; E. WALTON et al.: "Some analogues of 1-p-chlorobenzyl-5-methylindole-3- -acetic acid" * Page 1253, table I, compound no. 7 *	1	
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The present search report has been drawn up for all claims			TECHNICAL FIELDS SEARCHED (Int Cl 4)
			C 07 D 209/00

Place of search  
THE HAGUE

Date of completion of the search  
24-03-1986

Examiner  
MAISONNEUVE J.A.

### CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone  
Y : particularly relevant if combined with another  
document of the same category  
A : technological background  
O : non-written disclosure  
P : intermediate document

T : theory or principle underlying the invention  
E : earlier patent document, but published on, or  
after the filing date  
D : document cited in the application  
L : document cited for other reasons  
& : member of the same patent family, corresponding  
document